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ANTERIOR OCULAR TUBERCULOSIS.
GEORGE S. DERBY AND MAUD CARVILL

A CASE OF DETACHMENT OF THE ANTERIOR LAYERS OF THE IRIS.
MARK J. SCHOENBERG

THE TREATMENT OF THE COMMONER SYPHILITIC LESIONS OF THE EYE . . . . . J. G. HOPKINS

HOW PRIMARY GLAUCOMA MAY ARISE FROM DISTURBANCES IN THE PHYSICO-CHEMICAL FORCES WHICH REGULATE INTRA-OCULAR FLUID EXCHANGE . . . . . J. HERBERT WAITE

REMOVAL OF A NUMBER SIX LEAD SHOT FROM WITHIN THE EYE-BALL BY SPECIALLY DEVISED FORCEPS WITH THE AID OF THE DOUBLE PLANE FLUOROSCOPE . GEORGE H. CROSS

THE NUTRITION OF THE EYE . . . . . ANDREW RADOS

THREE CASES OF PROGRESSIVE AMAUROSIS OF RETROBULBAR ORIGIN. RECOVERY OF VISION WITH FOREIGN PROTEIN TREATMENT . . JULIUS WOLFF AND JOSEPH H. GLOBUS

OCULAR DISORDERS IN DEFICIENCY DISEASES
FRANCIS HEED ADLER

(Complete contents inside)

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ARCHIVES OF OPHTHALMOLOGY.

ANTERIOR OCULAR TUBERCULOSIS.[1]

A Group of Cases Followed Over a Period of Years

By Drs. GEORGE S. DERBY and MAUD CARVILL, Boston.

ORIGINALLY our scattering cases of ocular tuberculosis were treated in the Tuberculosis Class of the Massachusetts General Hospital Out-Patient Department. In 1909 a special class for treatment was established at the Massachusetts Eye and Ear Infirmary under the direction of one of us (G. S. D.) as ophthalmologist, and Dr. Theodore Eastman as internist, working in coöperation with the Out-Patient Department of the Massachusetts General Hospital. This class as such came to an end at the time of the war, but many of the individuals received further treatment in our Out-Patient Department. From the whole group, 130 patients with anterior ocular tuberculosis were selected for study. Of these we were able to locate 63.

This group is limited to anterior tuberculosis, largely cases in which the diagnosis could be made by the clinical appearance. It included a number of cases of severe phlyctenular disease, and many of our cases showed a sclero- or sclerosing keratitis. We stand flat-footed in the belief that phlyctenular disease, nodular scleritis, sclero- and sclerosing keratitis rest on a basis of tuberculosis, despite the views of Benedict and

[1] From the Teaching Service, Massachusetts Eye and Ear Infirmary, and the Department of Ophthalmology, Harvard Medical School.

others expressed at the 1926 meeting of this Society. In a number of cases scleritis of the nodular type was present alone. In a number of cases the iris and uveal tract were involved but in all of these the sclera and cornea were also affected. Uncomplicated iritis, uveitis, retinal and choroidal cases were not taken, as it was felt that at that stage of our knowledge of ocular tuberculosis the diagnosis could not be made clinically with sufficient exactness, the production of a focal reaction was often unjustifiable, and it is often absent. The advance in our knowledge of ocular tuberculosis, which knowledge is yet young, is well shown by the fact that there are many cases today of iritis, uveitis and disease of the choroid and retina where the diagnosis can be made clinically with a considerable degree of certainty.

Phlyctenular Keratitis.

It is interesting to note that in 33 of our 63 cases, or 53 per cent., the initial inflammation of the eye was a phlyctenular keratitis. In 13 of these, all but one of which had one or more recurrences, the following attacks of inflammation were phlyctenular keratitis. In the remaining 20 cases the following pathology was observed: in 3 episcleritis; in 6 scleritis; in 14 sclero-keratitis; in 4 uveitis; in 1 iritis.

Phlyctenular keratitis of a severe type was present alone in some of our cases. As they were stubborn to treatment in the Out-Patient Department, recurred even after frequent hospitalization, and severely threatened eyesight, they were referred to our class. Some of the cases of involvement of the sclera and cornea in one stage or another showed phlyctenular manifestation.

Diagnosis.

In this group of cases the diagnosis rested on the ocular findings, focal reaction to tuberculin (which often fails), on signs of tuberculosis elsewhere in the body, on ruling out other causes, on biopsy of the lesion, and on findings from guinea pig inoculations.

9 cases gave focal reaction, 4 of which had other signs of tuberculosis.

AGE OF ONSET GROUPED BY TYPE OF OCULAR DISEASE OF FIRST ATTACK.

Age	*Phylct. Keratitis*	*Sclero-Keratitis*	*Uveitis*	*Tubercular Keratitis*
1–10 First Decade	21	1		
10–20 Second Decade	8	4	2	3
20–30 Third Decade	2	1	3	
30–40 Fourth Decade	1	3	1	3
40–50 Fifth Decade	1	1	1	
50–60 Sixth Decade		1		
	33	11	7	6

	57 cases
no data to classify	6 cases
	63 cases

In 4 cases the biopsy showed tubercular lesions and 1 of them had other signs of tuberculosis.

In 1 case the inoculation of guinea pig was positive. This case had other tubercular involvement.

5 cases of children gave positive von Pirquet tests and had other signs of tuberculosis; 1 case, showing marked sensitivity to tuberculin injection, had tuberculosis elsewhere.

26 other cases of the whole group showed tuberculosis elsewhere in the body.

In 17 cases the diagnosis was made on the ocular findings alone.

It goes without saying that all cases were examined for foci

of infection, and when found these were eliminated as far as possible.

Race.

We realize that the Irish suffer extensively from tuberculosis and also that the Canadians in Boston are essentially Irish and have a high prevalence of tuberculosis amongst them. These people grouped together form in Boston the most important foreign-born group from the standpoint of number (97,276 in 1920), so it is not strange in a racial analysis of our 130 cases originally selected for this study that we find 81, or 62 per cent., belonging to this group. Of the native white of native parentage we find 20, or 15 per cent. Of the American negro there are only 2, or 1.5 per cent. This is surprising, for Boston has a large negro population (16,350, or 2.2 per cent of the total population), and the death rate from tuberculosis among these colored people is very high in Boston (460.5 per 100,000 in 1922). (It may be of interest to note here that in a group of 481 cases of phlyctenular keratitis that we have under observation, there are only 10 colored patients, or 2 per cent.). The remaining patients are about equally distributed among various foreign-born groups: Scotch 3; Swedes 3; English 3; Russians 2; Greeks 1; Lithuanians 1; Italians 3; Germans 2; no data 8.

Sex.

It is a well-known fact that tuberculosis affects the male element to a greater extent than the female. Here in a group of 130 cases of ocular tuberculosis we find 109 females or 84 per cent and 21 males, or 16 per cent. One reason for this may be the fact that men will often work with a tubercular infection in one eye while women are more often able and willing to take continued treatment.

Other Signs of Tuberculosis.

The other signs of tuberculosis present in this group of 63 cases were:

Involvement of the lungs in 19 cases.
Adenitis in 21 cases.
Tubercular ulcer of the leg in 1 case.
Tubercular sinus of breast in 1 case.
Tubercular synovitis in 2 cases.
Pleurisy in 3 cases.
Pulmonary hemorrhage in 1 case.
Abscess of ear in 1 case.
Abscess of lung in 1 case.
X-ray showed characteristic tubercular thickening of the mediastinal glands in 3 cases.
Skin lesions:
Miliary tuberculosis, 1 case.
Lupus, 1 case.
Scrofuloderma, 1 case.
1 case showed a double tubercular epididymitis, and an orchidectomy was performed.

Tuberculosis in Family.

There was a history of tuberculosis in the immediate family in 20 cases of 63, and of these patients, 14 had direct exposure in the home. Of the latter group 2 patients were brother and sister with a bad tubercular family history. Two maternal aunts died of phthisis, in the home; another aunt and the grandmother died of tuberculosis also. The brother had tuberculosis of the spine, and the sister tuberculosis of the spine and tubercular synovitis of the knee. Both patients showed severe phlyctenular keratitis.

In another family group are 3 cousins whose mothers were sisters. The family history was positive for tuberculosis. There was a history of direct contact in the homes. All 3 had phlyctenular keratitis in each eye. One had cervical adenitis and a healed pulmonary process. One of the others died of pulmonary tuberculosis and tuberculosis of the right kidney at the age of 14.

Severity.

In these cases we have seen all degrees of severity, from devastating inflammation with the loss of the eye, to the

abortive flurries showing only slight ciliary injection and disappearing in a few weeks. 16 cases could be classified as mild; 16 were moderate; 15 severe; and 16, very severe. Of the latter 16, 10 were hospitalized several times, all had many recurrences. Of their 32 eyes 2 were enucleated, 3 were blind, 5 had light perception, 16 could count fingers, and the remaining 6, which were the better eyes, had vision between $\frac{1}{10}$ and $\frac{20}{100}$. Of the 63 cases 21 were hospitalized and many of them several different times, 56 had recurrences, some as many as 16. In 42 cases both eyes were diseased; in 10 the right eye only, and in 11 the left eye only.

Vision of Both Eyes in 1926.

Full V = $\frac{20}{15}$, $\frac{20}{20}$, $\frac{20}{30}$	47 eyes
Good V = $\frac{20}{40}$, $\frac{20}{50}$, $\frac{20}{60}$	9 eyes
Practical V = $\frac{20}{70}$, $\frac{20}{100}$, $\frac{20}{200}$	17 eyes
Fingers	20 eyes
Light perception	5 eyes
Nil	5 eyes
Enucleated	3 eyes

We had a final vision on only one of the cases that died.

Of course, final vision in these cases is a meaningless phrase as the great tendency to recurrence is likely at any time to cause a reduction.

Complications.

Glaucoma developed in 4 cases, in which 4 iridectomies to relieve tension were performed. In 2 of these the eyes later became atrophied; in 1 the eye was later enucleated; and in 1 the results were good, the tension remaining normal and the vision $\frac{1}{10}$ four years later. Two optical iridectomies were performed.

Interstitial Keratitis.

As in our study of interstitial keratitis we found a few cases with tuberculosis present, as well as congenital lues, so here

we have 3 cases of congenital syphilis and interstitial keratitis which had tubercular lesions and later developed phlyctenular keratitis. Two cases with gonorrhea and syphilis had also tubercular findings, and 1 case showed a positive Wassermann but no symptoms of syphilis, but had tubercular findings elsewhere in the body.

Recurrence.

The majority of these cases show the characteristic course of tuberculosis, marked by chronicity and tendency to recurrence.

All but 7 of our cases had recurrences while under observation. Ten had 2 recurrences; twelve had 3; five had 4; nine had 5; four had 6; six had 7; one had 8; two had 9; the remaining cases having had respectively, 10, 11, 12, 13, 14, 15, and 16 recurrences. These attacks varied in severity from destructive inflammations, requiring treatment in the hospital for months at a time, followed by treatment in the Out-Patient Department for months longer, and in several cases resulted in the loss of the eye or phthisis bulbi, to mild cases with a slight amount of conjunctival and ciliary injection lasting over only a short period of time. The periods of time over which these attacks extended—that is, from the onset of the first attack to the time the eyes were white and quiet from the last attack—varied from 3 months to 45 years.

Long Periods of Quiescence.

Many of these cases have remained free from recurrence of inflammation over long periods of time. We have the data in 52 of our 63 cases of 69 quiescent periods, the duration of which varied from 3 years to 18 years. (Those of shorter duration than 3 years we are not considering.) In five instances the period free from inflammation was 3 years; in eight, 6 years; in three, 5 years; in ten, 6 years; in nine, 7 years; in six, 8 years; in four, 9 years; in six, 10 years; in three, 11 years; in six, 13 years; in three, 14 years; in one, 15 years; in three, 16 years; in one, 18 years. In 26 cases these were the periods between the time the eyes were white and quiet

from the last attack to the final check-up, and these of course will be of even longer duration. In all but 7 of these cases there was more than one recurrence.

With this it is interesting to compare the periods of quiescence after the removal of foci of infection in the series of cases of iritis reported by Brown and Irons.

Mortality.

The mortality among this group of patients is unusually high; 11 deaths among 63 patients, or 17 per cent. Six died of pulmonary tuberculosis, 2 of influenza, and 3 of cause unknown. It is of interest to note that the 6 deaths due to phthisis all occurred in patients who had had originally phlyctenular keratitis. Five of these had a family history of tuberculosis, and 1 direct contact with relatives with active tuberculosis.

Tuberculin.

Tuberculin has been freely used in the treatment of our cases. The preparation with which we have had the most experience is a bouillon filtrate prepared at the Saranac Laboratory and kindly furnished us. Old tuberculin has also been used to some extent. The initial dose in the majority of cases was $\frac{1}{100.000}$ *mg* increased as regularly as possible every five to seven days. The treatments in general were continued over a period of months. Thirty-two patients had a single series of injections, eleven had 2 series, five had 3, two had 4, four patients had 7 series of injections. In a few instances tuberculin has seemed to be of direct benefit to the patient. On the other hand, in 2 cases which we have observed, and both of whom later were treated by us after the damage had been done, we believe the tuberculin did great harm, and both of these patients lost the sight of both eyes. In the great majority of cases we believe that tuberculin injections have done neither harm nor good. We still use tuberculin in cautious doses, but principally on account of the mental effect on the patients. They feel that something is being done for them. We realize that these views on the

efficiency of tuberculin will be regarded as heresy by many ophthalmologists. Of the very numerous articles that appear on ocular tuberculosis from year to year, a considerable proportion are devoted to lauding the curative effects of tuberculin. Presumably most of these writers also give their patients the benefit of the standard methods of treating this disease, rest, fresh air, general hygiene, building up the patient, heliotherapy and the removal of possible foci of infection. Most papers, however, devote but few words to the general treatment and pages to tuberculin. The result is that the younger practitioners and others of little experience are apt to place too much reliance on this agent and too little on the methods that have stood the test of time in the treatment of tuberculosis. If tuberculin is such a valuable remedy why is it that with tuberculin injections it is impossible to cure animals inoculated with the disease? Why is it that the methods of using tuberculin differ so widely: some use minute doses and avoid any appearance of focal reaction, some insist that large doses should be used and a focal reaction sought. Why is it that many new preparations of tuberculin are introduced for which much is claimed? Why is it that many have become dissatisfied with tuberculin and are seeking help from other sources, light therapy, X-ray, radium and many other things?

Although it is very hard to find in the literature observations of cases over a long period of time, a few are available. Von Hippel observed considerable improvement in his cases from the use of tuberculin, but acknowledged that the question of recurrence of the attacks was of great importance and was not sufficiently taken into account.

Weigelin reports seventy-seven cases of anterior tuberculosis and uveitis observed over a duration of three to seventeen years, all treated with tuberculin. His conclusion was that the success of a tuberculin cure is not clearly proved. Most of his cases showed a transient improvement without the prevention of recurrence.

Igersheimer reports on three groups of cases: one observed over twenty years; one seven to seventeen years, mostly over ten; one over five years, and concludes that specific tuberculin therapy does not promise the success one might wish.

In most series the period of observation has not been suffi-

ciently long to allow the writers to draw valuable conclusions. We believe the most that can be fairly said of tuberculin therapy at the present time is that, in certain instances, it may help in cutting short the present attack. It does not prevent recurrence, and occasionally, and especially in inexperienced hands, it may do serious harm.

Summary.

It is excessively difficult to present a satisfactory analysis of our cases. This is largely due to the fact that, like tuberculosis of the lung, anterior ocular tuberculosis may be arrested, but it is incorrect to speak of a cure. One can never tell how severe a subsequent attack may be and how much the sight may be diminished. So until large series of cases have been followed throughout life we shall not know the truth about ocular tuberculosis. As far as we know our series of cases has been followed over a longer period than any other, if we except one of Igersheimer's series. Some have been under observation for twenty years, and none for less than ten. They average fourteen years. Before our class was organized in 1909 a number of cases had been followed intensively by one of us in coöperation with the general tuberculosis class in the Out-Patient Department of the Massachusetts General Hospital, and since the close of the war, although our own class has not been revived in the rather elaborate form of the previous period, yet these cases are now treated intensively by us and in a special group.

We believe that, incomplete as our figures are, the study of these cases carried out over this long period yields certain suggestive facts. Tuberculosis of the eye, like tuberculosis of the lungs, is a chronic disease which may be overcome for a time and held in abeyance, but is extremely likely to recur if the general resistance of the patient becomes lowered. The fact that our cases showed a mortality of nearly 10 per cent. from phthisis, although none of them showed active lesions in the lungs when we first took them into the class, may well give rise to thoughtful consideration. It is true that all these patients belonged to the hospital type, and had to earn their living, and thus were more prone to develop a low state

of general resistance. It may, however, be said that while in the class they were carefully instructed in methods of hygiene. They were living a life calculated to overcome the disease, and each patient was required to keep a book showing the temperature, pulse, number of hours spent in the fresh air, hours of sleep, and a list of their diet. Their home conditions were carefully supervised, and when found inadequate, the patient was referred for a variable length of time to a tuberculosis sanatorium. (14 of our cases were thus treated.) In spite of these efforts 6 of our cases died of phthisis.

The average attack of anterior ocular tuberculosis is usually, under proper hygiene, self limited, that is, the eye tends to recover from that particular attack, leaving a certain amount of damage behind. Sometimes the recovery may take place in two or three months, at times in eight or ten; again the disease may continue for well over a year. Then, depending on the general resistance of the patient, there is a period of remission; if the resistance be high this may last for many years, perhaps for the duration of life; if the resistance be not high the chances are that there will be a recurrence, possibly a mild one, possibly severe. The patient may develop tuberculosis elsewhere in the body. He may die of pulmonary tuberculosis or tuberculosis of some other part.

It seems to us that the principal lesson which is taught by the analysis of this group of cases which we are presenting, is that we have been holding ocular tuberculosis too lightly, and that in the future we must regard it more in the same class as the arrested case of pulmonary tuberculosis. Unless the resistance is kept high these cases are liable to a succession of recurrences in the eye. In addition they are peculiarly liable to develop serious tuberculosis elsewhere.

Few of our eye hospitals are equipped to give these patients adequate anti-tubercular treatment. Until they are we believe it is desirable that when possible these patients be sent to sanatoria for a number of months, not only for the treatment they get there, but also for the knowledge they obtain of the disease and the proper means to combat it. And especially we urge the view that these patients should be regarded as seriously affected with tuberculosis and treated

not only to cure the present attack, but to avoid recurrences, and so to build up their resistance that they will have a reasonable certainty of avoiding a more serious form of tuberculosis later on.

Summary of Fatal Cases.

Helen Ryan entered the Class in August, 1911, when 16 years old, with history of treatment in the House and Out-Patient Department for recurring attacks of phlyctenular keratitis since one year of age. Cornea O. D. shows scars of old phlyctenular keratitis, especially in the upper nasal quadrant, and some fresh phlyctenules in the center of the cornea. Practically the whole cornea, O.S., involved by old phlyctenular scars. In 1908 she had a positive reaction to the skin test. Adenoids were removed. Treated in Tuberculosis Class of Massachusetts General Hospital for a short time. Treated in the Eye and Ear Infirmary as in-patient, with tuberculin injections before entering Tuberculosis Class. Continued tuberculin injections for two and a half years. While a member in Tuberculosis Class spent six weeks at a convalescent home, gaining 15 pounds. Eyes were then white and quiet. The Wassermann reaction was negative. Had ten recurrences in the following six years, three of which were so severe that she was treated in the House. She has been to a State Sanatorium twice, once staying two and a half months and again for eight months. She gained in weight and health and her eyes were better. In 1913 had operation for spheno-ethmoiditis. In 1916 was treated at the Boston City Hospital for pneumonia. In September, 1915, had a fresh attack of phlyctenular keratitis and was given another series of tuberculin injections lasting over eight months. Wassermann negative. In 1916 had several flare-ups, also attacks of recurring hemoptysis. June, 1917, Massachusetts General Hospital found "nothing active," but "run down." In 1917 health good, good position with Cambridge Board of Health, continued in position two years. In 1920 left to go home to live with sister, where she worked very hard and almost immediately went down hill physically. Then went to State Sanatorium, where she later was in charge of the children at night. Became restless and left, returning to sister's. In 1924 returned to Massachusetts General Hospital with sore on heel, sinus, tuberculosis of os calcis, glands and swelling of left side of neck. Boston Consumptives' Hospital reports "nothing active found in lungs." February 4, 1925, Massachusetts General Hospital reports

"has never had definite active tuberculosis of lungs, but questionable condition," very suspicious of left apex. February 25, 1925, no change in glands, Wassermann negative, X-ray shows slight advance in lesion of lung. May, 1925, sent to State Sanatorium, stayed until November, 1925. Had two bad attacks of hemoptysis, returned home very ill, died May 19, 1926, at the age of thirty-one. Eyes became quiet when the lungs became markedly involved. V.O.D. $\frac{6}{200}$, V.O.S. $\frac{20}{200}$.

Hazel Cunningham entered the Class in May, 1909, at the age of two, with a mild attack of phlyctenular keratitis in each eye. Massachusetts General Hospital reported at this time: Lungs negative, teeth bad, tonsils large, heart negative. Diagnosis of miliaria made in Skin Clinic. Von Pirquet test positive in 1912. She had an earlier attack of phlyctenular keratitis in 1908. In 1915 she had another recurrence in both eyes; after the subsidence of the inflammation from this attack she never had any further trouble with her eyes. In 1910 she had pneumonia. In 1911 X-ray of lungs was negative. From 1912 to 1921 her health was good, she was able to continue with her class at school, and had reached the sophomore year in high school in 1921 when she was 14 years old. January 14, 1921: Massachusetts General Hospital reports "appearance of X-Ray of chest is characteristic of tuberculosis." Diagnosis of "Phthisis." She died at home in May, 1921.

The family history is interesting in this case. She was one of three cousins treated in our Class whose mothers were sisters. There is not only a history of tuberculosis in the family, but direct contact in the home, one of the patient's sisters—as well as an aunt, a sister of the patient's father—having died of tuberculosis in the home.

Celina Bisson entered the Class in July, 1910, when fourteen years old, with history of attack of phlyctenular keratitis in 1904 following measles. Report from the Massachusetts General Hospital: "Glands enlarged at edge of left breast, and in mastoid region. No signs of pulmonary tuberculosis." Treated in the Massachusetts Eye and Ear Infirmary as in-patient and on September 13th the eyes were white and quiet. She was then referred to the Class where tuberculin was continued over a period of two years. She had a recurrence of three months' duration in both eyes, in November, 1912, V.O.D. $\frac{15}{15}$, V.O.S. $\frac{15}{15}$. Patient's home was in Rochester, New Hampshire, where she died of pulmonary tuberculosis in October, 1919, aged 23, after an illness of several months. She had had frequent slight recurrences of her keratitis.

Mary Meldrum entered the Class with a severe sclero-kerato-uveitis in April, 1910, when 27 years old, with the history of first having had trouble with her eyes after an attack of measles when five years old. Since then has had recurrences every few years when "run down." Present attack began two weeks previous to her entrance into the Class. Very severe sclero-keratitis. Massachusetts General Hospital reports: "Slight cervical adenitis. Evidence of slight quiescent process at right apex." Tuberculin injections began April 23rd and continued through May, when patient went to New Hampshire. Returned July 1st, eyes worse. Referred to Massachusetts Eye and Ear Infirmary as in-patient on July 3, 1910. While in House under another service she received treatment with large doses of old tuberculin over a period of five months, after which she returned to the Class with the eyes much worse. There was a most destructive sclero-keratitis with uveal involvement which resulted in staphyloma in each eye terminating in phthisis bulbi. Small injections of tuberculin were given over a period of eight months. After 1911 patient worked with the Commission for the Blind for some time, and was at home for six or eight months before going to the sanatorium, where she was ill for five years before her death, from phthisis, at the age of 39, in June, 1922.

Fred H. Smith entered the Class on June 28, 1909, when he was eleven years old, with the history of having recurring attacks of inflammation in both eyes for two years. Patient under treatment at the Massachusetts General Hospital for Scrofuloderma and suppurating cervical glands. Von Pirquet was positive. At that time the right eye had two infiltrates in cornea, and a large phlyctenule, 3*mm* in diameter, 2*mm* from limbus. Four months later the eye had cleared up and was white and quiet, and the Massachusetts General Hospital reported: "Scrofuloderma, general condition good." August 31, 1909: Tuberculin injections started with 1–10,000*mg* and continued six months. May 15, 1912: Very severe attack. This was quieting down, when in June a deep abscess developed in the center of cornea. Tuberculin injections were begun again and continued throughout a year. Eyes white and quiet on August 6, 1912. February, 1913: Flare-up in left eye, which lasted three months. February 23, 1915: Very marked fresh lupus on right cheek and upper lid. Was treated for two months in sanatorium in Stoneham, skin lesions cleared entirely, and never had any further trouble with skin or eyes.

Worked as paper boy for several years. In 1916 began

to work inside. After a few months took cold in his back, and developed tuberculosis of the kidney and lungs. He was up and about the house until a few days before his death in May, 1917, at the age of 19, from tuberculosis of kidney and lungs.

Margaret M. Smith entered the Class March 25, 1913, when twenty-four years old. First inflammation of eyes followed an attack of measles in 1895 when she was six years old. Present attack of sclero-keratitis started two months ago. Massachusetts General Hospital reports: "Suspicious apices of both lungs." Tuberculin injections started March 25th, continued three months, when she entered a tuberculosis sanatorium, where she stayed six months, gained twenty-seven pounds, and looked in good condition. In 1923, when she was 34 years old, she died of phthisis, after several months' illness at home.

A CASE OF DETACHMENT OF THE ANTERIOR LAYERS OF THE IRIS.

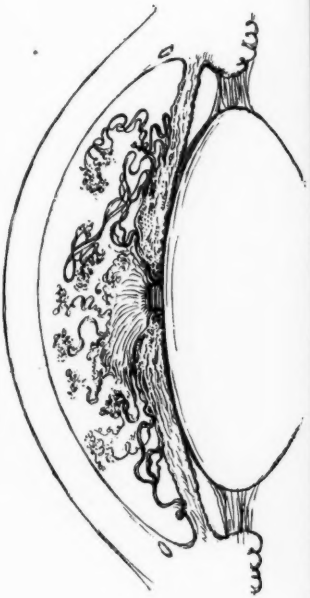
By Dr. MARK J. SCHOENBERG, New York.

(With two illustrations on Text-Plate XVIII.)

THIS report on an unusual type of iris rupture, due to trauma, following high diving, is interesting also to those who will happen to examine eye injuries of aviators who may have met with accidental falls from high altitudes. There is no denying that aviation is very rapidly becoming one of the main means of transportation and the number of accidents will not be smaller than that met with in other methods of locomotion.

Patient C. P. S., age 51, tall and a broad built man weighing 270 pounds, doing high diving at fairs and circuses for a livelihood, with a family and personal history of no consequence to the present condition, came to the Knapp Memorial Eye Clinic on January 7, 1926, complaining of failing vision in his left and only seeing eye. He attributes his trouble to one of his acts of high diving, which took place four months previously, when he climbed to the top of the rigging 104 feet above the tank. He remembers that his sight was perfectly clear. Then he jumped into a tank, 4 feet deep, 17 feet long, 11 feet broad. When he came up, he could not see, everything appeared black. He was led to the dressing room, and after some time, vision began to return gradually, but he could not see objects situated above the level of his head. Within a week, whatever vision he regained, remained unchanged until he came to the clinic. His vision remained foggy, but sufficient to allow him to perform his high diving acts. The record of this patient was a jump from a height of 186 feet, in 1¾ sec-

ILLUSTRATING DR. MARK J. SCHOENBERG'S ARTICLE, "A CASE OF DETACHMENT OF THE ANTERIOR LAYERS OF THE IRIS."



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onds. One and a half years before the accident he began to notice blue rings around the lights, but only at rare intervals.

The history of the right eye dates back 23 years, when, following a loop-the-loop bicycle act, it became suddenly blind. He was told later on, that he had a detachment of the retina and a luxated lens. He was operated on that eye, but without success.

Present condition.—Right eye slightly shrunken, tension normal, vision zero; old iridocyclitis with pupil obstructed by an old exudate.

Left eye.—Cornea clear, pupil slightly dilated, reacting very sluggishly to light and accommodation; lens clear; optic disk atrophic and deeply cupped, lower portion of the periphery of the fundus shows a large patch of chorioretinal atrophy with pigmented margins. The vision is $\frac{20}{100}$ with correction, and the field of vision contracted to about 5 degrees around the fixation point. Tension 40*mm* (Schiotz).

The iris of the left eye shows the following unusual changes:

First.—The anterior layers of the iris, mostly the temporal half of its ciliary region, seem to have detached, so that the layers containing the anterior surface and the parenchyma seem to have separated in places from the posterior pigmented layer of the iris.

Second.—There are several cracks or dehiscences in the iris tissue and through the pigment layer. These dehiscences, somewhat fusiform in shape, have a radiary direction.

Third.—In several parts, the radiary bundles that run from the pupillary to the ciliary margin of the iris are separated. Some of these bundles are attached only at both their extremities, others have one of their extremities —the pupillary or the ciliary—dangling freely in the anterior chamber.

Fourth.—Shreds of various shapes, length and thickness are seen hanging in the aqueous having their pedicle attached either to one of the bundles mentioned above, or to the extremely delicate veil-like tissue covering the anterior surface of the iris. Many of the loose ends of these shreds are covered by pigment, some very thickly crowded together—pale brown in color, some with dark brown, almost black, coarse granules. Seen with a loupe, the temporal portion of the anterior chamber looks like a small chamber of fluid in which miniature grayish bluish seaweed with its numerous ramifications floats freely. The pupillary margin shows a well developed, quite broad pigment

border, suggesting a mild ectropium uveæ. There is no tear or atrophy in this pigment rim.

There are no pigment or any other deposits on the posterior surface of the cornea—no ciliary congestion. The ocular tension receded to 30*mm* Hg after the use of a 2% solution of pilocarpin. The acuity of vision did not improve.

The unusual condition of the iris, the partial separation of the layers of the iris and the seaweedlike iris shreds floating in the aqueous, are no doubt of traumatic origin and must have appeared after a contusion of the eye, due to high diving. The absence of this condition in the right eye can be explained by the fact that the iris tissue in this eye is atrophied by the long standing iridocyclitis—which already existed before the detachment of the iris layers took place. No connection could be made between the glaucoma and the iris changes. It is very improbable that the severe iris lesion should be the cause of the increased intraocular pressure. The angle does not seem tightly obstructed by the dangling iris shreds, and though some of them are way at the periphery, this is seen only on the temporal side of the anterior chamber. Furthermore, if the iris tissue and crypts have something to do with the aqueous drainage, this should be rather facilitated by the teased and rarefied iris tissue. The sphincter pupillæ must have remained intact since it responded promptly to the pilocarpin and the pupil became very small.

The most plausible explanation of this separation of the iris layers is that the sudden trauma caused by an awkward motion during the high diving, must have suddenly forced the aqueous into the iris tissue, tearing apart the strands of its parenchyma and going through the entire thickness of the iris, in some places.

The interesting features about this case are: First, the unusual type of injury of the iris; second, its extent; third, the unusual kind of trauma. This form of trauma, a fall from great heights, will become a frequent accident as aviation will be one of the ordinary means of transportation in the very near future.

Up to the present time the vision with plus 2 sph. remained $\frac{20}{100}$ and the field contracted nasally 5–10 degrees beyond the fixation point, temporally 30 degrees, above and below 5 degrees; tension after use of pilocarpin 2%, 30*mm* Hg (Schiotz).

In the discussion of this case before the Eye Section of the N. Y. Academy of Medicine, Dr. P. Friedenberg expressed

the opinion, that the glaucoma is rather responsible for this peculiar atrophy and separation of the layers. On the other hand, Dr. Imre, Jr., reported on two cases which showed a separation of the anterior layers involving only one segment of the iris. Both patients were very old people (92 and 94 years of age) and had no glaucoma.

There are only a few cases of detachment of the anterior layers of the iris reported in literature. B. Drapkin (*Klin. Mon. f. Aug.*, Vol. 71, 1923) published the report on a case (female, 74 years of age), in which there was a lesion of this kind, occupying the lower part of the iris in the right eye and the lower and nasal segment of the iris in the left eye. The tension was normal. Drapkin believes that a tearing took place—in the iris. Whether this took place during the fœtal life, or later on, the author is unable to say. E. Sander (*Klin. Mon. f. Aug.*, Vol. 74, 1925) relates the case of an 81-years-old patient, who developed during two years, while he was under observation, changes in a segment of the iris of the right eye. The segment was situated between IV–VI o'cl. and the anterior layers of the iris looked as if a crochet needle had become entangled and had partly torn away the tissue, leaving shreds dangling freely in the aqueous. Sanders thinks this to be an acquired condition, due to a degenerative process in old age. There was no history of trauma, nor increase of tension. A. Schmitt (*Klin. Mon. f. Aug.*, Vol. 68, 1922) reports on a woman 74 years old, who presented in the lower and temporal quadrant of the right eye a separation of the anterior layers of the iris extending way over to the periphery. To Schmitt it looked as if the connective tissue had resorbed leaving only the blood vessels in the strands. The tension was normal. Both eyes had cataracts. The patient was suffering from a disease of the skin, neurodermitis circumscripta chronica, since childhood and from asthma since a few years.

Vogt (*Klin. Monatsbl. f. Aug.*, 1926, page 710, Vol. 77) presented before the Schweizer Ophthalm. Gesellsch. the patient reported by Drapkin. He called the condition "A case of senile iris apron" and described it in the following manner: "the pupillary ends of the strands of the anterior layers of the iris were poorly developed and had separated from the

underlying tissue. For this reason they floated freely in the aqueous for several years." Vogt followed and made drawings of the various changes that took place, and convinced himself of this progressive character. He attributes the location of the changes in the lower segment of the iris to gravity. The same author presented another patient, female 70 years old, who had a separation of the entire strand system of the anterior layers of the lower segment of the iris in an eye diseased for many years with iridocyclitis.

THE TREATMENT OF THE COMMONER SYPHILITIC LESIONS OF THE EYE.[1]

By Dr. J. G. HOPKINS.

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THE treatment of ocular syphilis is actually the treatment of systemic syphilis with ocular manifestations. To consider the problem of interest to the ophthalmologist, we must arrive at some ground of agreement as to the management of the systemic disease.

Management of Early Syphilis.—At the outset one must choose his objective. Is he to try to cure the disease or merely to control symptoms? As to secondary cases, we know that the majority of patients, if properly treated, remain free from symptoms for a long period, that their serum reactions remain negative, that they marry and have healthy children, and what is most significant in regard to their cure, that they apparently are again susceptible to infection, and if they reacquire the disease develop primary and secondary lesions just as would a patient who had not been infected. If it is true that we can cure early syphilis, or if there is even a possibility that it may be true it should be attempted in every case.

To effect such a cure, there are four groups of drugs at our disposal: the arsphenamines, mercury, bismuth, and the iodides. In regard to the first three, it is important to remember that they are known to be spirochæticidal in vivo if given in sufficiently large doses, and that in doses which are too small to

[1] Read before the Eye Section, the New York Academy of Medicine, April, 1927.

kill parasites these drugs appear to inhibit their growth. All of their clinical effects are not obviously due to spirochæticidal power, but our reasoning will be clearer and our therapy more effective if we bear in mind that this is the only mechanism of action which has been demonstrated. In the dosage usually employed, the arsphenamines are the most active spirochæticides, and there is little question that clinically they are the most effective of the three. In bismuth and mercury we have, however, two additional drugs of undoubted value, and it is generally accepted that better results are obtained by using them in courses alternating with courses of arsphenamine than in relying on the latter alone. There is no necessity of choosing between them, for in the long period of therapy which most syphilitics require there is time to administer all three remedies. Success depends not only on the drugs used, but on the plan according to which they are administered. Without entering into a discussion of details, we may mention certain principles to which it seems wise to adhere.

First. In early cases our treatment should be most intensive at the outset, as it is then that the spirochæte is most vulnerable and the patient most tolerant of the drugs.

Second. The giving of the drugs should be continuous, or as nearly so as possible. There is good reason to believe that much ground is lost by interposing rest periods between those of active therapy. It is possible that actual harm may be done in stimulating the development of lesions which have been irritated but not cured by the preceding treatment.

Third. Treatment should be prolonged, though just how long it is difficult to say. As relapses have occurred after trial of one system after another, the trend has been toward longer as well as more intensive and continuous treatment. For cases which have developed a positive Wassermann, a year may be considered the minimum and two years the optimum period.

Treatment of Tertiary Syphilis.—A more difficult question is that of the treatment of late cases. Certainly these are more resistant, but in a not inconsiderable number, if treatment is thorough and persistent, symptoms and serum reactions become negative and remain so for as long as the patients can be followed. It seems advisable, then, even in

late cases to bid for a decision, to begin cautiously and with small dozes but otherwise to follow much the same plan as in early cases, intensively for a year. If at the end of this period the serum reactions show no great weakening, it may be justifiable to consider a serological cure as impossible and to outline a scheme of treatment which is timed to prevent relapse, such as the giving of one course of treatment a year for an indefinite period, or the giving of two to four courses a year for three or four years.

Intraspinous Treatment.—Up to this point we have not mentioned intraspinous treatment. This is a subject as to which there is much controversy, although it is hard for one who has seen the benefits sometimes obtained to see how there can be any question as to its clinical efficacy. Certainly one cannot guide the treatment of a case of syphilis without determining the reaction of the spinal fluid by lumbar puncture. There are those who hold that if the reaction is positive all cases should be treated by the intraspinous method. A more conservative rule is to reserve intraspinal treatment for those who do not respond satisfactorily to the intravenous method, or in whom a prompt response to treatment is imperative.

Non-Specific Therapy.—There has been great interest in the past few years in non-specific therapy. The malaria treatment seems to have a definite if unexplained effect in general paresis, and has been used extensively in Finger's clinic in the treatment of early syphilis. At present, however, its use in any conditions other than paresis must be regarded as experimental and it has little bearing on the questions we are considering this evening. The line of research which it is opening up, however, may well lead to the introduction of methods helpful in all forms of this infection.

The Treatment of Syphilitic Iritis.—The foregoing discussion of syphilis therapy has a direct bearing on the management of eye lesions which will become clearer if we take a few of the more common conditions as examples. The most frequent eye lesion in the secondary period is iritis. As a rule, the iritis itself responds promptly to treatment. It is an indication, however, of systemic infection at a stage where it may be completely eliminated by proper therapy, and where, on the

other hand, inadequacy of treatment may forfeit forever the patient's chance of complete cure. Our chief responsibility, then, is not to clear up the iritis, but to eliminate the systemic infection. Prolonged intensive treatment according to the principles we have just discussed is essential.

This applies to iritis occurring in the secondary period. In tertiary cases, response is slower though usually satisfactory so far as the eye is concerned but the chance of curing the general infection is more remote.

Interstitial Keratitis.—A more common type of late syphilitic lesion in the eye is interstitial keratitis. Here the anatomical situation of the infection in an area not supplied by blood vessels makes the lesion peculiarly resistant to drugs. This has led to a pessimism in regard to keratitis which seems unwarranted by the results obtained. Interstitial keratitis requires the same intensive therapy one would give to any other late syphilitic lesion, with arsphenamine, bismuth and mercury in adequate doses, and potassium iodide pushed to the limit of tolerance. Among the first to call attention to the value of arsphenamine in these cases were two members of this Section, Denig[1] and Vandegrift.[2] We have all since seen patients who had been given mixed treatment without result clear up promptly under an intravenous arsenical.

In regard to the outcome in interstitial keratitis, our best source of information is probably the series of cases reported by Carvill and Derby.[3] In 100 untreated or inadequately treated eyes, they found 5% with total loss of vision or remaining light perception only. In 230 thoroughly treated, there were no such bad results. In the same series of 100 untreated eyes, there was some visual disability in 40%. In 230 thorough treated, there was disabling impairment of vision in only 23%. These results seem to understate the case for arsphenamine treatment, probably because no allowance was made for the degree of destruction of the cornea which had taken place before the first injection. On the repair of a damaged cornea, arsphenamine can be expected to have no effect, but it seems hardly to be disputed that it will arrest

[1] Denig: *Ophth. Record*, 1910, xix., 640.
[2] Vandegrift: *Med. Record*, Oct. 26, 1912, lxxxii., 760.
[3] Carvill and Derby: *Bost. Med. Surg. Journ.*, 1925, cxciii., 403.

the progress of the inflammatory process in the majority of cases.

Optic Atrophy.—There is room for much difference of opinion as to dosage, interval, and duration of treatment in iritis and interstitial keratitis, but there is no serious question as to the advisability of attempting specific treatment and little real reason to doubt of success in arresting the progress of the lesion. In atrophy of the optic nerve we meet with an entirely different situation, and there is probably no form of syphilis in which informed opinions on the question of treatment are so diametrically opposed as they are in this condition.

Opposition to specific treatment is based partly on doubt as to the possibility of cure, and partly on fear of adding to the damage caused by the disease.

In regard to the possibility of cure, the most we can expect is an arrest of the inflammatory process which is the indirect cause of the atrophy. Sometimes, as after other types of nerve injury, there is actual functional betterment even though there is no improvement in the objective signs. However, in cases which apply for relief before the damage is extreme, an arrest of the process is an important achievement.

As to the possibility of arrest many are absolutely pessimistic. In 1924, Fordyce[1] reported his results in 33 cases, seven of which became symptom-free with negative serological tests, and twelve of which obtained marked clinical improvement. He pointed out that cases due to basilar meningitis responded better than did those due to tabes. Since then the possibility of benefit in the former group has been more generally admitted.

As to tabetics, pessimism is more widespread, and Behr[2] in his most recent report concludes that it is useless to treat them. Some of Fordyce's improved cases were, however, clearly tabetic. Zimmermann[3] reported favorable results in a few tabetic cases, and attempted to differentiate the types of such atrophy which might respond to treatment. As examples of the unmistakable improvement which can sometimes be obtained, I would like to quote two cases.

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[1] Fordyce: *Brit. Journ. Derm.*, 1924, xxxvi., 47.
[2] Behr: *Münch. med. Wchnschr.*, 1926, lxxiii., 366.
[3] Zimmermann: *Arch. of Ophth.*, 1925, liv., 562.

The first is that of a young woman who came to the Presbyterian Hospital in 1921 with a history of failing vision for four years and typical lightning pains for three years. There was definite pallor of the optic discs with a concentric contraction of the visual fields. The ophthalmoscopic findings and high cell count suggested a basilar meningitis but the signs and symptoms of tabes were unquestionable. Four intravenous arsphenamine treatments had no effect, and intraspinous injections by the Swift-Ellis method were begun. After six of these, there was distinct subjective improvement in vision, and the spinal fluid Wassermann, which had been weakly positive, became negative. Four months later, she was given three more intraspinous treatments, and, as the spinal fluid Wassermann remained negative, was then put on intravenous treatment, which has been continued at intervals since. The blood Wassermann has remained weakly positive. Subjectively, there has been no deterioration in vision, which is better now than before she began treatment six years ago, and the last report on her eyes, a year ago, showed no change in the visual fields or in the eye-ground picture for two and a half years. The patient is probably not cured, but her optic atrophy is arrested.

Another case shows both the disastrous effect of insufficient treatment and the benefits of intensive treatment in atrophy due to a basilar meningitis. This patient developed an ophthalmoplegia, external and internal, in 1922. The reactions in both blood and spinal fluid were positive, but his vision was normal, and no change was visible in the optic discs. He received one course of eight neo-arsphenamine, and eight mercury injections, and the following year five more of neo-arsphenamine. He then stopped treatment because his eyes were apparently normal and he felt in perfect health. In 1924, eighteen months later, he returned with very marked visual disturbance, being able to read only the largest print, and with definite whitening of both nerve heads. Diagnosis of optic atrophy was confirmed by his ophthalmologist. After six intravenous injections of neo-arsphenamine there was no improvement, and intraspinous treatment was begun. For five months he was given Swift-Ellis injections every two weeks, with three bismuth injections between each intra-

spinal, making two treatments a week. Improvement was almost immediate following the beginning of this program, and by the end of the course, in May, 1925, his vision was $\frac{4}{4}$ in both eyes. He has continued intermittent treatment for two years. His vision remains at $\frac{4}{4}$ and there is no increase in the atrophy as determined by the ophthalmoscope. His blood shows a negative Wassermann and a weakly-positive Kahn, and his spinal fluid, a weakly-positive Wassermann. In this case, also, although the syphilitic infection has not been cured, the optic atrophy, which was perhaps provoked by the first brief treatment, appears definitely arrested by more intensive therapy.

I believe that these cases are not exceptional and that it must be granted that some cases of optic atrophy, including some of tabetic as well as those of meningitic basis, become arrested after intensive arsphenamine treatment. Such favorable results are, however, far from constant and many are deterred from attempting any therapy by the fear of accelerating the atrophic process.

All of the pentavalent arsenic compounds that have been introduced for the treatment of syphilis have at one time or another produced optic neuritis, and the danger of this is so widely recognized that all have been discarded except tryparsamide. The trivalent compounds, to which the arsphenamines belong, have been relatively free from such injurious effects, and the production of optic atrophy by arsphenamine in a previously uninjured eye has never been proved. However, in eyes with a pre-existing neuritis or with a pre-existing primary optic atrophy, arsphenamine has not infrequently appeared to cause damage. At least, cases which were progressing but slowly, or which had no subjective symptoms whatever, have degenerated rapidly after treatment was begun. Such effects have been observed also after mercurial treatment, and seem due rather to a provocation of the infection than to a direct injury to the nerve by arsenic. Doubtless in many instances where a disaster was attributed to arsphenamine it was actually due to a spontaneous acceleration of the disease. Nevertheless, the possibility of causing provocative or toxic damage is one which must be weighed in determining the advisability of treatment.

Decision as to our procedure depends on what alternative we must face. What happens to patients with optic atrophy who are not treated? This is not an easy question to answer. From textbooks one gains the impression that they all go on to blindness. One sees, however, cases that have apparently had some atrophy for years and that still have useful vision and it is possible that the prognosis is not so hopeless as is generally believed. If, however, it is utterly bad and these patients are doomed to complete loss of vision, the possibility of accelerating this process by treatment ought not to weigh against the possibility of definitely arresting it.

On the basis of the evidence at present available, it seems safer to treat than not to treat. One or two injections of bismuth or mercury should be given first and arsphenamine begun with small doses, in order to avoid provocative effects. The arsphenamine should, however, be rapidly increased to a maximum and should be given from the first by the Swift-Ellis procedure if the spinal fluid shows any abnormality.

Prophylactic Effect of Treatment.—The prevention of syphilitic lesions of the eye is more vital than the curing of them. Observations on the development of ocular lesions in patients who have been previously treated, has led to unwarranted pessimism in regard to the prophylactic effect of treatment. There is no doubt, however, that the large majority of such lesions are met with in patients who have never been treated. Carvill and Derby in their series of 200 cases of keratitis found only 10 which had had any previous treatment and in none had the treatment been adequate. Of 25 cases of iritis treated at the Vanderbilt Clinic during the past year, only four had had previous treatment; of 34 cases of keratitis, only three. Of 25 cases of optic atrophy, none had had adequate treatment early in their disease, and only three any considerable amount at any time before the development of their eye lesions. On the other hand, it is by no means exceptional to observe eye lesions in previously treated patients, but the important point is that these patients though treated were not cured. From evidence to which I have referred before, it is fairly well established that in the majority of patients who have had intensive treatment early in the disease, symptoms disappear, serum reactions become and remain negative, and

no further symptoms develop in the eye or elsewhere. This is as true of congenital cases treated in infancy as it is of acquired cases treated early in the secondary period, and holds for some cases treated later in the disease. If such a clinical cure is not attained, we can have no certainty that treatment will prevent the development of ocular or other manifestations of late syphilis. A few injections of salvarsan, or a year or so of mercury, will seldom if ever prevent future lesions, and may indeed provoke them. That fact should be merely an incentive to sufficiently vigorous and prolonged treatment of early cases and does not in the least discourage our hope that such treatment will prevent the development of eye lesions.

SUMMARY.

1. Patients with iritis occurring in the secondary stage should be treated intensively with neo-arsphenamine, bismuth, and mercury for two years. The governing consideration in their treatment should be not the healing of the eye lesions but the clearing-up of their general syphilitic infection.

2. Patients with interstitial keratitis or tertiary iritis should be treated with the same drugs, and should also receive iodides. Continuous intensive treatment should be carried on for a year and continuous or intermittent treatment for two years further.

3. Treatment should be attempted in all cases of incomplete optic atrophy, beginning with bismuth or mercury and soon adding neo-arsphenamine, at first in small but in rapidly increasing doses. The Swift-Ellis routine should be used unless the spinal fluid is normal. If exacerbations of the symptoms follows the arsenic treatment, it should be stopped for a while and again begun with caution.

HOW PRIMARY GLAUCOMA MAY ARISE FROM DISTURBANCES IN THE PHYSICO-CHEMICAL FORCES WHICH REGULATE INTRAOCULAR FLUID EXCHANGE.[1]

By Dr. J. HERBERT WAITE, Boston, Mass.

(With two figures in the text.)

(Concluded from the September number.)

II. *Fluid exchange within the normal eye.*

A. *The hydrodynamic theory* assumes that the aqueous comes from the ciliary processes, flows forward through the pupil, and escapes through Schlemm's canal, always following along the line of descending pressure. In two dozen recent communications, Seidel (7) defends the beliefs of Ludwig, of Leber, and of many other noteworthy advocates of this theory, and he ascribes to hydrodynamics the dominant rôle in fluid exchange within the eye.

A growing opposition to the hydrodynamic theory during recent years finds its culmination in the extreme views of Magitot (8) and of Hamburger (9). Both of these workers believe that the aqueous is essentially stagnant in the normal eye. Magitot believes that the aqueous originates as a dialysate from neuroglia cells, and that intraocular pressure is regulated through the erectile tissue reservoir of the choroid counterpoised against the incompressible fluid cushion of the aqueous-vitreous. Hamburger contends vigorously that the water-tight valve action of the iris upon the lens completely seals the posterior from the anterior chamber; that fishes lack both ciliary body and canal of Schlemm; and that the horse with ten times the aqueous content of man has no semblance

[1] Read before the New England Ophthamological Society, April 12, 1927.

of a canal of Schlemm. By the hydrogen peroxide method of Magnus and Stübel, Hamburger claims to have demonstrated numerous iris lymphatics, by which fluid may escape. Türk (10), and also Berg (11) have demonstrated that the visible currents in the aqueous are merely convection currents, because they are brought to a complete standstill by the application of a body temperature water bath to the cornea.

The hydrodynamic theory has been built around a supposed low pressure in Schlemm's canal, low because of its cloistered position behind the scleral spur and the pectinate ligament. While no one has ever succeeded in measuring the pressure in Schlemm's canal, recent careful measurements by Weiss (12), Lullies (13), and Duke-Elder (14) would indicate that the pressure in all exit veins, vortex, central retinal, and anterior ciliary, is higher than the intraocular pressure. If these observations can be definitely confirmed, then the hydrodynamic theory will have to be abandoned.

Upon clinical and experimental grounds it may be accepted that the blood pressure within the intraocular capillaries and veins is maintained at a higher level than the intraocular pressure, or else circulation would cease. It is well known that circulation continues even in high pressure eyes. After incising one of the vortex veins of a cat's eye, and upon raising the intraocular pressure through injecting fluid into the vitreous, Leonard Hill (15) observed that blood continued to flow from the incised vein until the intraocular pressure was made to equal the arterial pressure of the eye, when all circulation stopped.

In view of what has been said about fluid exchange in living organisms, it does not seem justified to reduce fluid exchange within the normal eye to a simple matter of plumbing, nor does it seem justifiable to ignore the fact that the eye does contain semi-permeable membranes separating fluids which have different osmotic values.

B. *The membrane equilibrium theory* for intraocular fluid exchange is just coming into being, pieced together from available scraps of information which the new-born science of colloidal chemistry is able to give. Baurmann (16), Dieter (17), and Duke-Elder have recorded their beliefs that aqueous is an ultrafiltrate, but they adhere to the idea that

Schlemm's canal is the chief outlet for aqueous. Serr (18) clings to the secretory theory for aqueous production, and yet commits himself to the belief that osmotic processes account for its removal. If one desires to be consistent, one must seek to explain both elaboration and reabsorption of aqueous upon the same general laws.

In the eye as elsewhere in the body, the forces concerned in the exchange of fluid between blood and aqueous are the semi-permeability of the capillary walls and of the ciliary epithelium, and as the result of this the osmotic pressure of the blood colloids, balanced against the hydrodynamic blood pressure.

There are two forces which tend to prevent ultrafiltration from the blood, namely, the osmotic pressure of the blood colloids which has a nearly constant value of 30 millimeters of mercury, and the intraocular pressure which has a variable value somewhere between 10 and 25 millimeters of mercury in the normal eye. It is unusual for the intraocular pressure in the normal eye to mount higher than 10 or 12 millimeters of mercury. One may then express the sum of these two values, 40 millimeters of mercury, as a critical level. If the capillary blood pressure rises above 40 millimeters of mercury, there must be a movement of water from blood to aqueous, while if the capillary blood pressure falls below this level, there must be a movement of water from aqueous to blood.

This brings us to the very important question of blood pressure within the uveal capillaries, and one that has never been solved. Weekers (19), Magitot (20), and others have pointed out that merely pricking the iris will shoot the intraocular pressure to a high level, which requires at least fifteen minutes for its subsidence. Even if this were not so, it would be extremely difficult to find capillaries in the normal iris, into which one could insert a microcannula. Neither slit-lamp examination, nor microscopic examination of histological material will reveal red blood cells within iris vessels as a rule, unless the iris is diseased, or unless there is obstruction to free venous outflow from the eye. In the face of an unknown anatomy and physiology of the uveal capillaries, it does not seem unreasonable that there may be two pressure levels represented here:

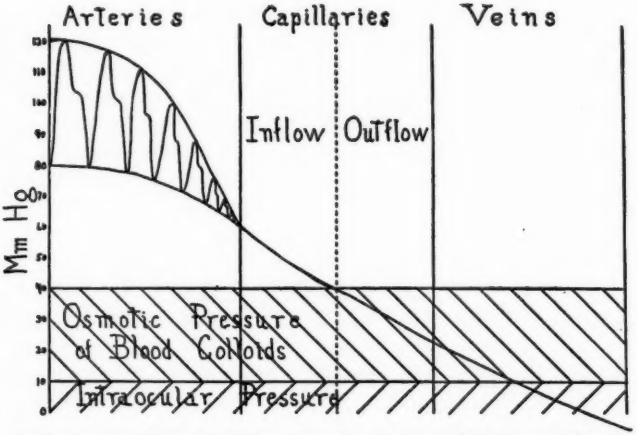
1. *The high pressure capillaries: those of the ciliary body.* Ligation of the long posterior ciliary arteries gives marked hypotony with degeneration of the iris and cornea, as cited by Wagenmann (21), and Siegrist (22). Coats (23) cites a case in which thrombosis of these vessels produced the same picture. Duke-Elder assumes on the basis of similar source and size, that the long posterior ciliary arteries must carry a mean pressure similar to that of the central retinal artery, which by actual measurement was found to be in the cat around 76 millimeters of mercury (88 systolic, 64 diastolic). Since the wide capillaries of the ciliary processes are closely connected with the major circle, it does not seem unreasonable to assume that they may carry a pressure higher than 40 millimeters, the critical pressure for ultrafiltration in the normal eye. If such a pressure can be demonstrated, one must come to the opinion that aqueous is of the nature of an ultrafiltrate, because it contains nothing which is not already present in the blood.

2. *The low pressure capillaries: those of the iris*, and also *the canal of Schlemm which osmotically is merely a giant capillary.* Parsons (24), in describing the vessels of the iris, states "that iridic arteries are unusually thick-walled in the adult, and difficult to inject." The iris arteries are very tortuous, and they have small caliber; hence it does not seem unreasonable to assume that the blood pressure has fallen below 40 millimeters of mercury by the time the blood has reached the capillaries of the iris. Seldom is an iridectomy in a normal eye attended by hemorrhage.

If the pressure within the iris capillaries keeps above the intraocular pressure, they are not collapsed, and circulation continues through them. If the pressure within them does not equal the critical pressure necessary for ultrafiltration, namely 40 millimeters of mercury in the normal eye, then aqueous will be sucked up into the blood stream, in all the capillaries and venules of the iris. That such a process aids in the escape of aqueous seems to be borne out by what follows the injection of india ink into the vitreous. Weekers (25) and others have observed that most of the carbon particles are deposited over the entire anterior surface of the iris, and over

the pectinate ligament. Nuel and Benoit (26), and Behr (27) have corroborated this observation in the human eye.

Rarely does the canal of Schlemm contain blood. It is not known whether it contains normally any more protein than does the aqueous. It is well known that the canal communicates directly through open collaterals with vessels containing whole blood, and therefore the canal of Schlemm can act as an osmotic viaduct for the passage of aqueous into the blood stream of the collaterals.



Reference to *Chart I* will show the theory in graphic form: within the high pressure ciliary capillaries the preponderance of blood pressure over osmotic pressure gives rise to the aqueous as an ultrafiltrate; within the low pressure capillaries of the iris the preponderance of osmotic pressure over blood pressure gives rise to osmotic removal of aqueous; in health inflow equals outflow.

III. *Fluid exchange within the glaucomatous eye.*

The cause of primary glaucoma has been sought in vain in increased general blood pressure, in obstruction of the vortex veins (Birnbacher and Czermak 1886), in cavernous atrophy of the optic nerve (Schnabel 1892), in hydrophilism (Fischer 1909), in fibrosis of the pectinate ligament (T. Henderson 1911), in disordered pump action of the ciliary muscle upon the scleral spur (A. Thomson 1911), in disturbed

sympathetic innervation, in imbalance between intraocular and intracranial pressures, and in endocrine and other disturbances.

If primary glaucoma were due to altered condition of the blood, one would expect to meet with simultaneous involvement of both eyes far more commonly than it occurs. Scalinci (28) and others have found the hydrogen ion cencentration of the blood, vitreous, and aqueous practically identical. Tron (29) has found sodium and potassium present equally in aqueous and vitreous, but in greater concentration in the blood. Hertel (30), and Duke-Elder (31) have demonstrated experimentally in animals that ocular pressure responds temporarily to changes in the osmotic condition of the blood, but Serr (32), and Hertel and Citron (33) have found that the blood of glaucoma patients has practically the same osmotic values as the blood of normal patients.

The natural deduction from studies such as these is that the cause of glaucoma must be sought in the eye itself. Ever since Mauthner in 1881 first pointed out the presence of a shallow anterior chamber in glaucoma patients before the onset of increased intraocular pressure, human ingenuity has taxed itself to learn the cause of this shallowing. Priestley Smith in 1891 advanced the idea, which he has since given up, that the growing lens might account for the shallowing of the anterior chamber. Czermak in 1897 first called attention to the relationship between swelling of the vitreous and shallowing of the anterior chamber. Fischer (34) attempted to explain swelling of the vitreous through increased acidity, while Meesman (35) more recently points out that increased alkalinity of the vitreous may cause the same result. But Schmelzer (36) and others have shown that the vitreous in glaucoma is maintained at practically the same hydrogen ion concentration as is the vitreous in health. Nordenson (37) has hypothesized a progressive senile impermeability to water of the hyaloid and of the anterior layers of the vitreous. Priestley Smith and Troncoso have assumed that the pores of the vitreous membranes might become clogged with red blood cells and protein molecules.

Of all theories extant, the one which best fits the clinical chronology of glaucoma is that of Verhoeff (38). He believes

that mucinous degeneration of the epithelium over the pars plana of the ciliary body releases mucin into the vitreous; that the mucin-charged vitreous becomes less permeable; that the anterior chamber therefore becomes more and more shallow until the iris comes in contact with the cornea; and finally that intraocular pressure increases with blocking of the filtration angle. He states that nearly all eyes with primary glaucoma show evidence of present or past obstruction at the filtration angle, when tissue sections are examined under the microscope.

Verhoeff does not concede, and properly, that pressure in in the vitreous chamber can ever exceed pressure in the aqueous chamber by an amount greater than the inherent elasticity of the iris-lens-zonule diaphragm. The elasticity of this diaphragm can readily be measured by observing the effect upon the depth of the anterior chamber, following elevation of vitreous pressure, provided both aqueous and vitreous chambers communicate with manometers through needles of equal bore. In the freshly enucleated human eye, studied in this manner by Verhoeff, the anterior chamber never fails to be shallowed when vitreous exceeds aqueous pressure by one millimeter of mercury, and to become obliterated when this difference amounts to two millimeters of mercury.

While the trend in modern glaucoma theories tends to explain increased intraocular pressure on the basis of a blocked filtration angle, the blocking brought about through an increase in the volume of the vitreous, no theorist has yet claimed that his theory explains all cases of primary glaucoma. The more we learn about fluid exchange in living organisms, the less are we willing to reduce glaucoma to so simple an explanation as obstructed drainage. Until definite experimental data are forthcoming, any glaucoma theory can be no more than a mere statement of probabilities, but it should include all factors which are known to be operative. It seems therefore that no glaucoma theory can afford to ignore the semipermeability of the ocular membranes, and coincidentally the osmotic pressure of the blood colloids. It should be realized furthermore that these problems fall beyond the range of the compound microscope.

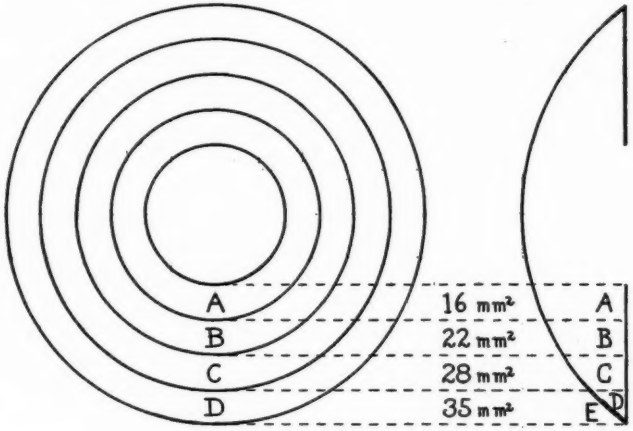
If we may assume that normal intraocular fluid exchange is the resultant between the several forces enumerated above, then we may assume that abnormal intraocular fluid exchange (hypertonus) must be the result of an imbalance between these forces, manifesting itself as an increased inflow of fluid into the eye chambers, or as a decreased outflow of fluid from the eye chambers, or as a combination of both tending to perpetuate a vicious cycle.

1. *Increased inflow.* Greef (39), and Collins (40) have shown experimentally that the ciliary epithelium is raised up in blebs by an albumin-rich fluid, following the sudden evacuation of aqueous. It seems that nature has covered the ciliary body with a triply reinforced layer (Bruch's membrane surmounted by two layers of epithelium), ***designed to be highly impermeable to blood proteins.*** If this membrane loses, even in a small measure, its high impermeability to blood protein, there must be not only a leakage of blood protein but also an increased inflow of water and other constituents of the blood into the chambers of the eye. So long as the normal outflow channels are adequate to drain off this increased inflow, there is no increase in the intraocular pressure, but only an increased rate of fluid movement through the chambers of the eye. Whenever inflow exceeds outflow by ever so little, there must be at once a condition of increased intraocular pressure, but not necessarily a shallowing of the anterior chamber. Relatively copious drainage through a filtering cicatrix would seem to indicate that some cases of primary glaucoma are due to excessive inflow.

Failure to find albumin in the aqueous by means of coagulation tests does not necessarily disprove this theory. Jasinski (41), LoCascio (42), and Goldschmidt (43) have established the presence of proteolytic ferments in the aqueous, and Jasinski has demonstrated in aqueous the presence of tryptophan and of a positive Biuret test. Therefore, it would be more to the point to compare the total nitrogen of glaucoma aqueous with the total nitrogen of normal aqueous. However it is well known that certain protein-split products such as histamine have a powerful dilating effect upon capillaries, and it requires little imagination to see how dilated

capillaries could hasten the escape by diffusion from aqueous into the blood of the smaller protein-split molecules.

2. *Decreased outflow.* Assuming that aqueous escape is not purely hydrodynamic by way of Schlemm's canal, but rather osmotic by way of the iris capillaries and venules, and through Schlemm's canal into its blood-containing collaterals, we must seek to explain how these outflow channels may be reduced. Osmotic interchange must be reckoned in terms



Surface of Zone A—15.71mm^2
Surface of Zone B—21.99mm^2
Surface of Zone C—28.28mm^2
Surface of Zone D—34.55mm^2
Surface of Zone E—34.55mm^2 (pectinate ligament)

of the surface of the interface. The interface, where blood meets aqueous, must be the combined surface of all capillaries and venules of the iris stroma, and of the cross section area of all collaterals to Schlemm's canal. The computation of this interface is one of the important problems for the future. For the present, we must be content with only an approximation of this interface, obtained by computing the surface of various zones of the iris, and of the pectinate ligament, each one millimeter wide.

As the anterior chamber becomes shallowed in glaucoma, it will be seen that the interface becomes obliterated from the

periphery. Mechanical contact between zones D and E practically eliminates $\frac{89}{184}$ or more than half of the available outlet surface, while elimination of zones C, D, and E removes $\frac{97}{184}$ or nearly three-fourths of the total outlet surface. Perhaps neither mechanical contact nor permanent tissue union between iris and cornea completely seals off the esmotic escape of aqueous, but greatly reduces it.

If we assume that the shallowing of the anterior chamber is the outcome of an increasing volume of the vitreous, we must show how the vitreous volume can be increased in glaucoma. If Nordenson's assumption is correct, that the hyaloid and the anterior lamellæ of the vitreous grow with advancing age less permeable to water, it would appear that glaucoma should be more prevalent, should be bilateral, and that it should progress without attacks steadily toward blindness, if untreated. It is well to remember that many cases of primary glaucoma show recurrent attacks, in which increased intraocular pressure is attended by simultaneous shallowing of the anterior chamber. It is suggested, therefore, that the periodic increases in the volume of the vitreous in glaucoma may be due to a shower of blood protein which leaks through an imperfectly functioning ciliary epithelium, and which becomes caught within the colloidal meshwork of the vitreous. This protein-charging of the vitreous no doubt would be favored by the intimate union between the vitreous and the epithelium of the pars plana of the ciliary body. While it is conceivable that protein may be eventually swept out of the vitreous through ferment action, it is fairly clear that the large molecules of the ferments might not have free access to the proteins which are enmeshed within the colloidal vitreous.

3. *Vicious cycle.* Both Leber and Parsons represent the iris blood vessels as emptying back through the venæ vorticosæ. If so, then every increase in intraocular pressure must compress these vessels against the inelastic sclera, and in this way bring about an elevation of their contained blood pressure, and hence of the blood pressure within the iris capillaries. Since the blood pressure within the iris capillaries affects the level at which intraocular fluid exchange can take place, elevated blood pressure within the iris capillaries necessitates a higher level of pressure for intraocular fluid exchange.

The considerations of both normal and abnormal intraocular fluid exchange suggest many problems, which are in urgent need for solution, such as the anatomy and the physiology of the capillaries of the iris and ciliary body, the physicochemical behavior of the vitreous, and the normal and abnormal permeability of the ciliary epithelium.

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REMOVAL OF A NUMBER SIX LEAD SHOT FROM WITHIN THE EYEBALL BY SPECIALLY DEVISED FORCEPS WITH THE AID OF THE DOUBLE PLANE FLUOROSCOPE.[1]

By Dr. GEORGE H. CROSS, Chester, Pa.

(With two illustrations on Text-Plate XIX.)

CONFRONTED by the many failures to remove a non-magnetic foreign body from the vitreous chamber it was the necessity of this case, the patient having only one eye, which led to the designing and construction by the writer of a special pair of forceps which when used in conjunction with the double plane fluoroscope successfully removed the pellet of shot without loss of vitreous or serious damage to the eye except the necessary scleral incision.

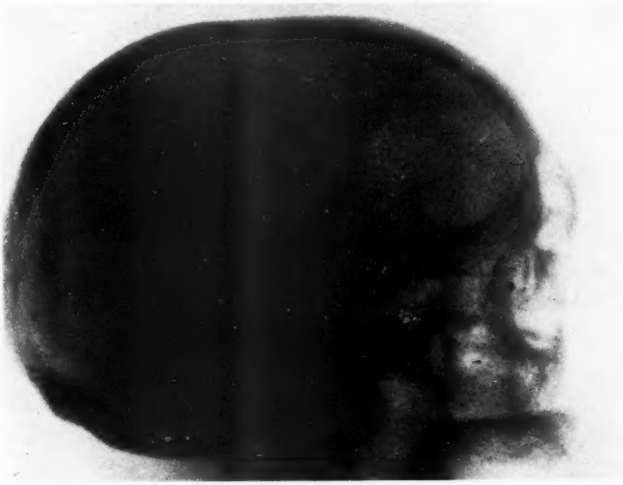
Case Report.

J. B., age 51, on November 6, 1926, while in his yard in the country was shot in his remaining eye by a rabbit hunter. The pellet of shot passed through the upper eyelid on a downward course entering the sclera, above the cornea, about 8*mm* from the limbus lodging in the vitreous chamber about 12–15*mm* back, 6*mm* to the temporal side and 8*mm* below as shown by the X-ray films. It was impossible to see the shot with the ophthalmoscope or by direct illumination, on account of the vitreous hemorrhage. S. = M.H. His right eye was enucleated twenty-five years ago following a penetrating wound of the globe by a fragment of metal while working as a machinist.

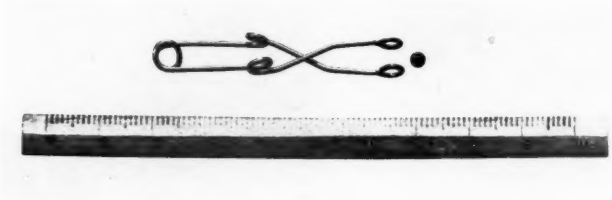
Four days later following a consultation with Dr. Willis

[1] Read before the meeting of A. O. S., Quebec, June, 1927.

ILLUSTRATING DR. GEORGE H. CROSS'S ARTICLE, "REMOVAL OF A NUMBER SIX LEAD SHOT FROM WITHIN THE EYEBALL BY SPECIALLY DEVISED FORCEPS, WITH THE AID OF THE DOUBLE PLANE FLUOROSCOPE."



X-Ray photograph showing position of number six lead shot in the vitreous chamber.



Specially devised forceps used for removing shot.

Manges, the Roentgenologist, at Jefferson Hospital, Philadelphia, it was decided to make an attempt at removal with the aid of the fluoroscope on November 12th. In the meantime three different instruments were thought out and constructed, the successful instrument being a pair of cross-action forceps made of number 18 German silver wire with the ends flattened, bent in the form of a circle and filed out to fit a number six lead shot.

Through the kindness and courtesy of the late Dr. William M. Sweet, the patient was admitted to his ward in Jefferson Hospital, Philadelphia, and the operation was performed in the fluoroscopic room under local anesthesia.

Dr. Manges carefully located the patient on the fluoroscopic table so the two beams of light would cross at the position of the foreign body and demonstrated the presence of the foreign body in the eyeball, noting when the patient moved his eye its change of position in both the vertical and the horizontal plane. After opening the conjunctiva and placing sutures through the cut edges to hold them apart, an incision about 6-8*mm* long was made through the exposed sclera with a Graefe knife, below the insertion of the external rectus muscle. The forceps were entered through the incision, turned at right angles so the action of the forceps would be in the line of the incision while the tips were placed over the approximate position of the lead shot, as located on the X-ray film. The speculum was then removed on account of its interference with the fluoroscopic shadows, all lights turned out and the next steps of the operation carried on in darkness except for the slight reflection from the fluoroscope. Dr. Manges then directed the location of the tips of the forceps as the patient endeavored to hold his eye in a fixed position. When the forceps were in alignment with the shot they were released and grasped the shot but it slipped away; immediately the tips were reopened and on the second attempt they closed securely over it. The lights were turned on and the patient's eyelids opened, the forceps were turned at right angles so as to bring the tips of the forceps in line with the scleral incision and removed from the eyeball. The lead shot was found securely held in the forceps that were made to fit it. The conjunctiva was sutured over the incision, the eye bandaged and the patient put to bed.

This case report would not be complete without due credit to Dr. Willis Manges for his valuable assistance and very essential and skillful coöperation; had he not been able to locate the shot and accurately direct the movement of the forceps with the aid of the double plane fluoroscope, our results would not have been a success.

Observations.

It is essential that the instruments for this work be very short so they will permit the fluoroscope to be brought close to the patient's eye; long instruments are too cumbersome, they prevent a good view of the eye and if touched by the fluoroscopic plate upset the patient by causing pain and may cause serious damage to the intraocular structures.

It is of great importance that the instruments be self-acting so that the moment the foreign body is engaged in the instrument the operation is practically over; there are so many complications and obstacles to overcome that it would be impossible to juggle the foreign body on the end of a spoon or maintain even pressure on ordinary forceps so the foreign body would not be dropped out or squeezed out during the necessary manipulation in withdrawing the instrument from the eyeball.

An ambidextrous operator has a decided advantage in handling cases of this character. In this particular case there was no alternative but to operate left-handed; it was the patient's left eye that was involved and it was necessary to stand at the head of the table, there being no other position available. The fluoroscopic operator required two sides of the patient's head and the X-ray tubes took up the other two sides; this left but one place for the surgeon nor was there room for an assistant. A speculum or any object which is capable of casting a shadow or interfering with the shadow of the foreign body or the forceps cannot be used. Despite these handicaps there was no loss of vitreous.

Vision after operation equalled light perception; an exudate filled the pupillary space so that no view of the fundus was obtainable.

THE NUTRITION OF THE EYE.[1]

By Dr. ANDREW RADOS, Newark, N. J.

THE nutrition of the eye varies in many respects from the usual nourishment of other tissues. The eye is unusual, due to the fact that the cornea and lens are without blood vessels under physiologic conditions, and therefore the nutrition of these tissues is subject to special laws. Nature had to provide a complete transparency of the optic media. Therefore, the contents of the anterior and posterior chambers are of utmost importance, and to follow our topic closely we must consider the biology of these fluids. The question is interesting not only as a physiological problem, but is important in explaining the solution of numerous conditions of the eye which we meet in our every day practice. In this connection I want to mention the well-known fact that various inflammatory conditions of the iris and ciliary body begin with a slight myopia which is due to acute hyperemia of the tissues. It will be demonstrated later that the normal aqueous has a certain refractometric index, and in cases of exudations this index shows a marked increase due to higher amount of albumen. The transitory hypermetropia in cases of diabetes, the decrease of intraocular pressure in diabetic coma, and the entire question of glaucoma are closely related to this topic. Our knowledge of the composition, source, circulation and carrying off of the aqueous has all been based on the experiments of Leber, which have proven that the aqueous is produced by the epithelial covering of the ciliary processes. The aqueous is slowly circulating from the posterior chamber

[1] Read before the Eye, Ear, Nose and Throat Section of the Academy of Medicine of New Jersey, Newark, November, 1925.

through the pupil into the anterior one and is carried off by Schlemm's canal and veins on the anterior surface of the iris, the latter being, however, of minor importance. Leber's explanations were widely accepted, due to the fact that they explained many clinical features. We know of the existence of congenital aniridia, a condition characterized by absence of the iris and by presence of the anterior chamber filled with aqueous. In other words, the intact ciliary body is producing in this kind of congenital anomaly a normal product which fills out the space behind the cornea. Furthermore the secretion mentioned above is in accordance with embryologic findings that the anterior chamber is only developing when the pupillary membrane is about to disappear. Thus the ciliary secretion has a possibility to filtrate into the anterior chamber through the holes in the membrane. According to Hamburger, the anterior chamber is already filled by aqueous before the pupillary membrane begins to disappear.

The secretion of the ciliary body explains secondary glaucoma in cases of interruption of the circulation between these chambers and the bulging forward of the peripheric parts of the iris in so called iris bombé which follows occlusion of the pupil. Secondary glaucoma, however, develops only after a lapse of time, and iris bombé can be produced without a circular adhesion in cases of aplasia of the peripheric part of the iris. In complete circular synechia the posterior chamber production, together with the blocking of the current, offers a satisfactory and obvious explanation.

Certain facts contrary to the results of Leber came to light in recent years which led Hamburger to take for granted that the production of the aqueous is in no case a secretion of the ciliary epithelia, and that there is no current from the posterior into the anterior chamber, but that the production of aqueous is only due to cellular activity of the iris. Hamburger believes that not only is there no current of the secretion through the pupil, but that there is no communication between these two chambers at all. He tries to prove and demonstrate the closing of the pupil by bringing neutral-red into the anterior chamber when there is a red discoloration exclusively in the pupil; after the enlarging of the pupillary space by an artificial coloboma the staining shows up just within the bor-

ders of the area exposed. According to Hamburger, the ciliary body produces only a very small part of the aqueous, and although it is indispensable, the ciliary body is negligible from the standpoint of aqueous production. Moreover, the aqueous is not produced by secretion of the ciliary epithelia, being chemically absolutely different in composition from the secretion obtainable in cases of obvious ciliary secretion after paracentesis of the cornea. He believes that the physiologic rôle of the ciliary body is in no case the secretion of the aqueous but the protection of the cornea and iris from the pressure of the lens during accommodation.

The aqueous and vitreous have only one analogy, the spinal fluid. Their production, composition, and biological qualities show many corresponding qualities.

The aqueous is as clear as water, of neutral or slightly alkaline reaction, with a specific gravity of 1.0034–1.0060. The amount in human beings is around 0.23*cc*. After the removal of the normal aqueous the chamber will be refilled in a relatively short time. We see, especially after cataract operations, that the refilling of the chamber takes 10–15 minutes and this fact taught us to wait with expression of the cortex until the chamber is restored.

The normal content of the anterior chamber is very poor in albumen, if it contains any at all. This question is very hard to decide. The most useful method for the determination of albumen in such small quantities is the examination by refractometer. The Abbe-Zeiss refractometer used in my experiments gives a refractometric index of about 1.3350, but 1.3360 of the refractometer is equivalent to an 0.17% albumen solution. In other words, the normal aqueous has less albumen than the amount mentioned. Naturally in these lower values even the refractometer no longer is reliable, and therefore we want to state only the fact that the amount of albumen under normal conditions never exceeds 0.17%.

The fact that the normal aqueous is free of albumen has been known for a long time, and furthermore, due to experiments on small animals, it was established that on restoration of the aqueous, the albumen content was much richer. The restored aqueous is characterized by a comparatively high refractometric index, which shows a direct proportion

to the time elapsed between the first and the second puncture of the chambers and the amount removed at the first puncture. The larger the amount of aqueous removed, and the shorter the time between first and second aspiration, the higher was the refractometric index found in my experiments

I found[1] the same value in different animals (rabbit, cat, dog, horse and cow) but the amount of albumen was always far behind that of the blood-serum. The following is a typical example. The first aqueous of a rabbit gave a refractometric index of 1.3351 (less than 0.17%). I removed the whole amount, and a second puncture of the same eye after an hour gave a refractometric index of 1.3430 (4.087%). After puncture of the anterior chamber I found in numerous experiments that the increase in albumen in the aqueous is pronounced during the first hour; after 5–6 hours there is a decrease in the albumen content, and in twenty-four hours the physiologic condition is completely restored. We find similar conditions in all animals; these findings are the basis of the Leber theory. The ciliary epithelia act like glands producing the normal aqueous. The second aqueous has a higher amount of albumen due to cystic changes in the ciliary body. And indeed the histologic examination of such eyes proved the presence of big cysts under the epithelial layer filled out by a fluid rich in albumen. Some of them ruptured, emptying their contents into the posterior chamber. Leber took for granted that similar conditions prevail in human beings too, and this belief was accepted in all the text books for many years.

I had opportunity in recent years to examine human eyes under conditions similar to those of my experiments on animals. Only eyes with no pathologic changes in their anterior parts could be used, such as eyes with sarcoma in the back part or with embolism of the central artery. In cases of the former the eye had to be removed anyhow, in the latter the puncture and the rapidly diminishing intraocular pressure are of a therapeutic value. The examination of human aqueous revealed the surprising fact that the human aqueous does

[1] A. Rados: Untersuchungen über die chemische Zusammensetzung des Kammerwassers des Menschen und der Tiere. *Arch. f. Ophthalm.*, Vol. 109, 1922, pp. 342–386.

not give an increase of the refractometric index after puncture and removal of the first one. ***The second one is just as poor in albumen as the first one.*** The interesting fact namely the difference between human beings and animals, has been proved. The physiologic aqueous is a solution very close to the so-called ionizable one. In animals its removal produces a regeneration which contains higher amounts of albumen and therefore is a colloidal solution. The non-physiologic or colloidal solution shows all gradations from a finely dispersed to a coarsely dispersed one, up to a solution containing fibrin corresponding to the disturbance of the permeability of the cells. Thus the aqueous loses the physiologic homogenity, the colloidal solution lacking transparency. The increase of the albumen content is disproportionate to the increase of the salts, and therefore the albumen is not dissolved in the aqueous. In cases of inflammation of the anterior part of the globe the human aqueous is in a colloidal instead of an ionizable solution and the succeeding aqueous after the removal of the former is still richer in albumen.

The production of the aqueous is a function of the ciliary epithelium. If we paralyze the function of these cells by sodium fluoride it will result in lack of production. The intact ciliary epithelium prohibits the simple filtration of the blood-serum. Under physiologic conditions the aqueous differs in every respect from the serum, only the so-called colloidal approaches the serum in similarity. The ciliary epithelia show a double function. The ionizable solution is due to dyalization, the colloidal solution to filtration. The first is lacking in complement, amboceptors and haemolysins of the serum and permits the passage of certain salts in definite amounts only, the importance of which is obvious. The salts bind water molecules and thus regulate the intraocular pressure and transparency of the lens. The experiments of Hertel illustrate the connection between the amount of salt of aqueous and vitreous and intraocular pressure. He showed that by injecting hypertonic salt solution hypodermically or intravenously the intraocular pressure is greatly reduced. It is a well-known fact that the lens, put in a less than 1% saline solution shows a marked swelling and in a more than 2% solution, shrinking; in other words, an increase of the

salt content due to some disturbance of the ciliary epithelium may be the cause of cataract formation, and some authors thus explained cataract due to naphthalin intoxication, or tetany.

There can be no question about the ciliary origin of the aqueous. Such a complicated and delicate mechanism cannot be regarded as a simple filtration through the wall of blood vessels, or similarly, it cannot be due to the activity of different cells. The permeability of the cells under physiologic, and even pathologic conditions, demonstrates an elective function. The presence of certain stains as fluorescin in the anterior chamber does not prove the participation of the iris in the production of aqueous, as fluorescin appears in the anterior chamber if the stain is injected into the arteries after death.

The Ehrlich line proves only that there is a constant current existing in the anterior chamber dependent upon the different temperatures within the chamber, the posterior wall being of a higher temperature than the anterior one. The presence of a steady current can be easily demonstrated by examination with the slit-lamp.

The aqueous is the nutritive agent of the cornea and lens. For health, its normal consistency is absolutely necessary. In pathological conditions the aqueous changes to a colloidal solution and contains strange components. I have demonstrated in the colloidal solution the presence of bilirubin which explains the apparent greenish discoloration of the iris in cases of iritis.

In the nutrition of the lens the aqueous is not the sole factor, the vitreous is also concerned with the nourishment, especially that of the posterior pole.

The normal course of the metabolism of the lens is regulated by means of the capsule. The normal metabolism of the lens is very important on account of preserving its transparency. The capsule has not only a passive, but an active rôle in the nourishment of the lens. The lens of the living eye becomes cloudy after a wound of the anterior lens surface, and a cataract is produced. Massaging causes changes in the cells of the capsule, and cells are then not able to prevent the lens from imbibing aqueous. Many proteins like

fluorescin are diffused in the lens through the anterior and posterior capsule. The anterior capsule prevents the entrance of foreign substances more than the posterior capsule does. The exchange between the lens and the surrounding fluids is an exceptionally slow one, but after entering the lens they disseminate between the lens fibers and later enter the cells and remain within the lens for a very long time. For example, lithium salts stay for weeks in the lens, and the fluorescin discoloration of the lens remains for many months. Certain chemical substances cause a cataract formation if they are introduced in certain amounts. Of these we know the action of naphthol and naphthalin. The cataract in cases of naphthalin intoxication is not caused by a direct action of the naphthalin on the lens substance but is due to changes in the aqueous by pathologic changes in the ciliary body. The latter changes are hyperemia, swelling and cyst formation in the epithelial layer. The question is not quite established how substances circulating in the blood enter the lens. It is a fact that changes in the osmotic pressure of the surrounding fluids also act on the lens. We have to accept the possibility of a cataract formation due to loss of water if we introduce so much salts that we produce a substantial change in the water balance of the tissue fluids. Doubtless the water attraction of certain substances is not the sole factor in cataract production. Certain substances are able to provoke changes in the different ingredients of the lens, for example, the mechanism of such substances acting on the protein contents of the lens.

The pathologic metabolism of the lens reveals the presence of the most different substances within the lens. The change in the permeability permits not only sugar to enter but different bile salts dissolved in the aqueous and the vitreous. The so-called cataracta brunea and nigra have been clinically known for a long time, but only in recent years has the development of microchemistry given us the exact evidence of their ætiology. The chemical composition of the lens proteins proves the presence of albumoid, α and β crystalline and albumen, and membranine in the capsule. These proteins are biologically absolutely different from the other proteins of the body. In serological experimentation, especially by

means of precipitation, it can be demonstrated that the lens possesses not a species but a constitutional specificity. This constitutional specificity gives a singular position of the lens protein in the organism. The posterior surface of the lens is in contact with the vitreous and thus the vitreous has the same importance as the aqueous in the nutrition of the lens.

The chemical composition of the vitreous is very similar to the aqueous with the exception of a few important differences. The specific gravity of the vitreous is 1.005–1.009 having a similar amount of proteins as the aqueous, but we find traces of mucin, glutin, mucoid and nucleon. The sodium chloride content is inconsistent, but always higher than that of blood-plasma, and thus it represents a fluid hypertonic in relation to it. We find strange substances circulating in the blood first in the region of the ciliary processes in the vitreous, from which point they spread over the entire vitreous, and finally we find them around the optic disc. This fact demonstrates the steady current within the vitreous; furthermore, it designates the course from the ciliary body toward the posterior pole. The carrying off is substantiated through the vitreous canal and the perilymphatic spaces of the blood vessels. The soluble substances enter the vitreous by way of diffusion and are eliminated from the vitreous by the same process. The extirpation of the ciliary body is followed by atrophy of the vitreous showing that the ciliary body is the chief factor in the production.

Is the vitreous the product of a secretion? It cannot be a true secretion having no newly formed substances which have not been present in the blood. Secretion is always characterized by the formation of specific ingredients like ptyaline in the product of the salivary glands.

The vitreous, the same as the aqueous is produced by dialysation. Every change in the normal composition can easily be detected. The normal vitreous is quite clear. The increase of proteins, the presence of grossly dispersed protein molecules can be detected by the ordinary examination and especially with the slit-lamp. The presence of cholesterin crystals or sodium phosphate cause the well-known synchisis scintillans.

Pathologic changes within the vitreous are liable to dis-

turb the normal lens metabolism and cause a posterior cortical cataract due to pathologic metabolism on the posterior lens pole. The cases of complicated posterior cataract due to uveitis or inflammatory changes in the vitreous belong to this group.

THREE CASES OF PROGRESSIVE AMAUROSIS OF RETROBULBAR ORIGIN. RECOVERY OF VISION WITH FOREIGN PROTEIN TREATMENT.[1]

By Dr. JULIUS WOLFF, Ophthalmic Surgeon of Mt. Sinai Hospital, New York, and Dr. JOSEPH H. GLOBUS, Adjunct Neurologist, Mt. Sinai Hospital, New York.

(With twelve illustrations in the text.)

Introduction.

THE intravenous administration of foreign protein is not a new form of therapy in medicine. The favorable results obtained from this therapeutic measure in subacute forms of inflammatory diseases are now well recognized. Of late it has been employed with good effect in various eye conditions and Allen (1) reports its beneficial application in diseases such as corneal ulcers, keratitis and various forms of uveitis. Its mode of action is still not entirely understood, and it is not the purpose of this paper to go into discussion of the physiologic effects of foreign protein and how it brings about the desired results. A good summary of the present views on the subject is contributed by Mueller (2). Our aim is to bring before you three unusual clinical cases with uncommon manifestations in which a foreign protein has been employed with strikingly favorable results.

All of these cases have points in common which permit grouping them as a single entity. Each of this group was characterized by an insidious onset of progressive loss of vision; each case developed in the course of the disease central

[1] Read before the Section of Ophthalmology, New York Academy of Medicine, January 17, 1927.

scotomata, which widened progressively and led to almost complete loss of vision; in each case there were visual field changes in the nature of hemianopsic disturbances. In none of the three cases were there signs of a localizable, expansile, intracranial lesion. None of the cases showed evidence of increased intracranial pressure and all of the three cases failed to react to any form of treatment except typhoid vaccine injections, the latter bringing about complete or almost complete restoration of vision.

Case Records.

Case 1.—B. H. W., aged 38, married. Family history negative. In her past personal history we find the following facts: In childhood she had a severe form of malaria. At a later date she had a severe attack of grippe. Somewhat later a tuberculous gland in her neck was removed. She was married in 1909 at the age of 20 and gave birth to a normal child the following year. In 1912 she had a spontaneous miscarriage. During that year she had what was considered a neuritis in the right arm. In 1913 she suddenly developed double vision without known cause, lasting about six weeks and disappearing without treatment. In 1915 she gave birth to another normal child. Both of her children are well and normal in every respect. In the early part of April, 1917, she complained of mild attacks of dizziness of one months' duration. An eye examination at the time revealed no fundus changes, normal pupillary reactions and intact extrinsic muscles of the eyes, with vision O. U. $\frac{1}{2}^{5}$.

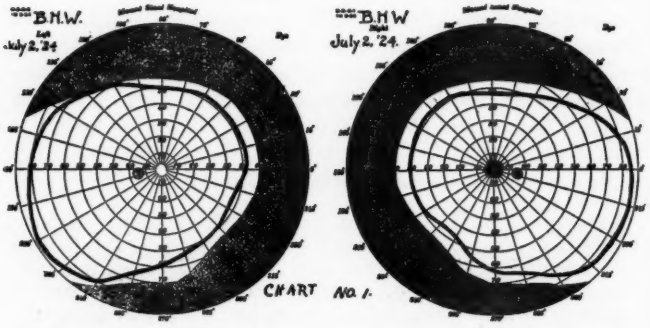
On October 7, 1918, she returned for an eye examination, complaining of slight headache, transient diplopia, slight unsteadiness in gait and impaired handwriting. Eye examination disclosed normal vision, normal fundi and normally reacting pupils. Only on testing with a red glass was some diplopia elicited, which suggested a very slight paresis of the right inferior rectus.

She remained well up to December, 1921, when on account of the recurrence of transient attacks of dizziness she appeared for another examination. Nothing abnormal was found.

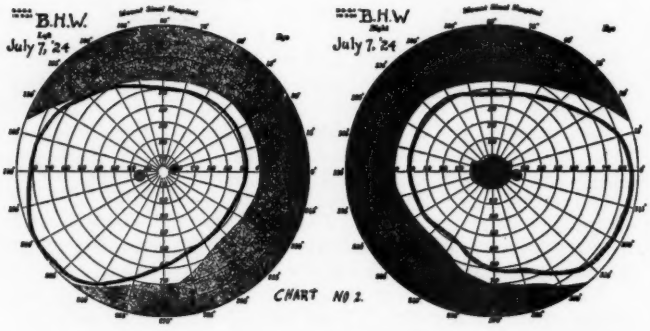
In 1922 she passed through an acute illness which lasted for several months and which was diagnosed as a form of angioneurotic edema.

The middle of June, 1924, marked the beginning of visual disturbances. She complained of blurred vision in the

right eye. On testing it was noted that the visual acuity in that eye varied from $\frac{1}{10}$ to $\frac{1}{20}$ and there was a very small central scotoma. Vision in the left eye was $\frac{1}{10}$; the pupils fundi and all the extrinsic muscles were normal. The



impairment of vision progressed gradually and on July 2, 1924, an examination revealed a central scotoma extending a few degrees to the right and to the left of fixation, with a small almost absolute area for color. (Chart 1.) The following days marked rapid progress in the impairment of vision in the right eye with the central scotoma growing



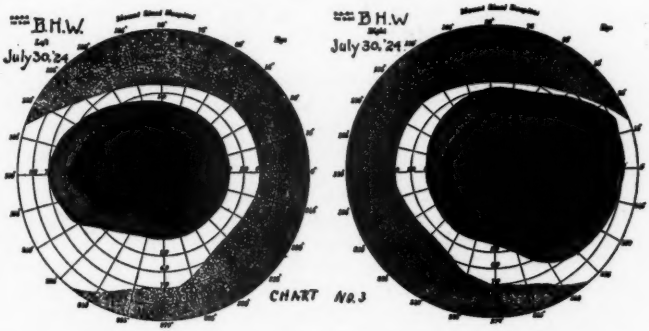
rapidly in size; so that on July 7, there was an absolute area extending on the nasal side to the 12 degree circle, on the temporal side to the 15 degree circle, and above and below to the 12 and 15 degree circles respectively. (Chart 2.) Vision in the right eye was reduced to counting fingers eccentrically. The vision in the left eye showed mild im-

pairment due to the appearance of a small relative scotoma a few degrees to the nasal side of the fixation point. In both eyes the fields for form were good.

An X-ray examination of the skull gave negative results; X-ray of the teeth revealed no foci of infecton.

Blood chemistry as well as the blood and cerebro-spinal fluid Wassermann tests were negative, as were also the urine tests.

About the middle of July a neurological examination failed to disclose any positive findings and an ethmoidectomy was suggested on the ground that the condition was a form of retrobulbar neuritis due to sinus infection. This was done, but without benefit to vision.



Somewhat later another neurological examination revealed vague objective findings which led to the diagnosis of multiple sclerosis. Still searching for the primary seat of infection, a second dental examination was made and several teeth were found infected. They were removed, cultures of streptococcus viridans were obtained, a vaccine was prepared and used. This, however, did not arrest further development of new symptoms, while vision continued to decline; so that on July 29 vision had diminished to such an extent in both eyes that fingers could hardly be counted at a distance of two feet, and then only in the peripheral field. The absolute scotoma in each eye was very large, being surrounded by a relative area (Chart 3). The limits of the visual fields, tested with a 4*cm* square object, were still only moderately constricted, except that in the right eye the absolute scotoma reached the periphery between one and two o'clock. In spite of this the pupils reacted to light and the fundi showed only a suspicion of a temporal pallor.

With the progressive loss of vision there began to appear other manifestations and an examination by Dr. Globus revealed a definite right peripheral facial paresis, right external rectus weakness, right footdrop, absent abdominal reflexes, but active deep reflexes, with the right KJ and AJ more active than the left, a right Babinski sign, and right ankle clonus. The patient complained of dizziness and almost total loss of vision. His findings were interpreted as an inflammatory lesion of the brain in the form of subacute encephalitis. A neurosurgeon was then called in to rule out a possible neoplastic lesion. This examination substantiated all the findings of Dr. Globus in every way except for the facial weakness, which he regarded as central in type. He was inclined to the diagnosis of a neoplastic cerebral lesion, believing that a tumor was somewhere in the mid-frontal region. He suggested operative interference.

The patient was then transferred to Mt. Sinai Hospital for further observation and an eventual craniotomy. In the hospital her condition remained at first unchanged and with the two diagnostic possibilities in mind, it was thought a ventriculography would possibly throw more light on the character and the seat of the lesion.

On August 8, a ventriculography was performed without giving additional information as to the character and seat of the lesion. Following the ventriculography the patient developed aphasic manifestations mainly in the nature of paraphasic speech disturbances. The following day, August 9, an exploratory craniotomy was performed. The findings were not satisfactory; they consisted of a slight increase in the subdural fluid and the suggestion of an area of diminished resistance in the depth of the frontal lobe. This led the surgeon to suggest the diagnosis of a cystic glioma.

Following the operation the patient showed a marked decline in her condition. Vision now was totally lost. Her speech was unintelligible, paraphasic, she misused words; her phrases were incoherent; her answers irrelevant; she perseverated. She now developed bilateral ankle clonus, bilateral Babinski sign and marked ataxia in all extremities in addition to signs she presented before.

The mental deterioration progressed rapidly, so that in a few days she became totally demented, became noisy, unmanageable, unclean in her habits. She could not understand commands, her speech was nothing but a few meaningless loud sounds.

She could not longer be cared for in the hospital and had to be taken to another institution. The one selected was a

sanatorium for the care of mental patients. The first three days in that institution were marked by further deterioration in her mental and physical condition. Her activity was now reduced to a vegetative state. She was blind, completely aphasic, untidy, and completely disoriented. At this point the diagnosis was once more reconsidered and in the belief that we were dealing with an instance of an atypical form of encephalitis, foreign protein therapy was suggested and administered. On September 7, she received her first injection with typhoid vaccine intravenously. The dose was 2 million organisms in saline suspension. It was repeated three days later; following the second injection improvement was noticed. Her general condition was better and she began to say a few words. From now on each succeeding administration of the vaccine was followed by a distinct change for the better in her physical as well as mental state. She gained power in the paretic leg so that she could stand up and walk about with some support. Her vision began to return and mentally she showed clearing intellect, better judgment and some insight into her condition. The improvement was uninterruptedly progressive and at the end of five weeks she left the institution and returned home in a remarkably improved state of health.

When seen on November 22, 1924 by Dr. Wolff vision in both eyes was $\frac{1}{10}$, though somewhat unsteady and easily exhausted by strong light. The disks showed slight temporal pallor. There was no absolute scotoma, but a relative hemianopsia for red in the left fields, mainly in the upper portion. The field limits for form were almost normal in both eyes. She was still receiving treatment with apparent favorable results, and when seen on April 10, 1925, vision in the right eye was $\frac{1}{5}$ and in the left eye $\frac{1}{10}$. On June 29 in the same year the right eye showed $\frac{1}{5}$ and the left eye $\frac{1}{5}$ minus. From now on her condition remained stationary and satisfactory. She returned to a normal life, did fine needle work, reading, cared for the house, did her shopping, visited friends, entertained friends and assumed the full responsibilities of a wife and mother. In the early part of January, 1926, she was suddenly taken ill again. This time she complained of dizziness, vomiting several times, her gait became staggering and she experienced double vision again. On examination she showed bilateral nystagmus, more to the right, marked external rectus weakness, impaired hearing in the right ear, ataxia in both arms and legs, staggering gait with falling to the right. This was regarded as a recurrence of the meningoencephalitic process, mainly in the nature of an external

hydrocephalus. She was given again six injections of typhoid vaccine and with the first injection improvement set in and progressed rapidly, so that after the sixth injection she was well again, and remained well up to the present time. A recent examination showed little beyond generalized hyperreflexia, right Hoffman sign, increased right ankle jerk and markedly diminished abdominal reflexes. The optic discs showed slight temporal pallor and there was a relative quadrant hemianopsia in the upper left fields beyond the five or ten degree circle.

CASE 2.—G. E., male, aged 51, business man. His family history presents no facts bearing on his recent illness.

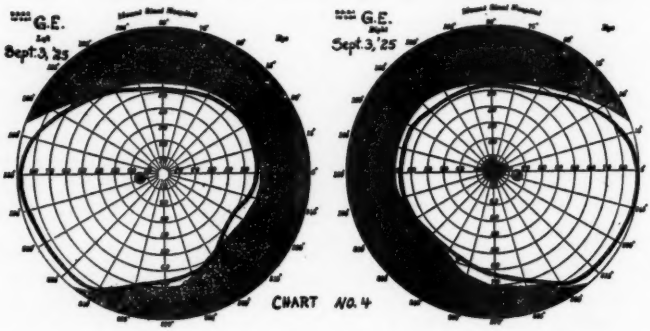


CHART No. 4

In his past personal history we find that he indulged moderately in tobacco, but that he indulged in alcoholic beverages steadily and sometimes to excess. He was treated by Dr. Wolff occasionally for minor ocular ailments and for refractive errors since 1909. The last examination, before the appearance of symptoms, took place on June 17, 1925. At that time corrected vision in both eyes was normal and no changes were noted in the pupillary reactions, in the eye excursions and in the fundi.

His present illness began within a short time after the last examination. When seen on September 1, 1925 he complained of impaired vision in the right eye. On examination it was found that V.O.D. was $\frac{15}{200}$, V.O.S. was $\frac{15}{15}$. There were no visible lesions which would account for diminished vision in the right eye, except for an apparent slight elevation of the upper outer quadrant of the disk and for a slight blurring of the corresponding part of the margin of the disk. This appearance remained unchanged and proved to be of no significance. Tension was normal

and the exophthalmometer readings of both eyes were alike. The field for form was normal, but there was a central absolute scotoma, about eight degrees in width. (Chart 4.) X-ray examination of the skull showed no pathologic changes. Examination of the teeth was negative; urine and blood Wassermann tests were also negative. His general systemic condition was normal.

Impairment of vision progressed and suspicion was directed to the accessory sinuses. The ethmoid, sphenoid and antrum were opened on the right side and a small amount of pus was found in the latter. The operation did not help the vision.

High colonic irrigations were also tried, without favorable influence. On the contrary, an eye examination (September 14, 1925) showed further decline in vision, as the patient could only count fingers at ten feet with his right eye. The left eye had $\frac{1}{18}$ minus.

At the suggestion of another ophthalmologist, seen in consultation, the optic canals were X-rayed, but were found to be normal in size.

The vision continued to fail, so that with the right eye he could but count fingers at seven feet, while in the left eye V. was still $\frac{1}{18}$ minus.

At this time two diagnostic possibilities were considered: A neoplasm in the head of the right optic nerve or sinus disease. Potassium iodide and mercury were administered at the suggestion of another ophthalmologist who was consulted, but it brought no results.

Dr. Globus was then consulted and his examination revealed but few objective findings. There was marked hyperreflexia with the left KJ more active than the right, marked tremor of the fingers, a suspicious Babinski sign on the right, diminished upper and absent lower abdominal reflexes. These findings were of a disseminated character and hence excluded a neoplasm as the causative factor. They pointed in the direction of a diffuse cerebral lesion, not unlike the so-called subacute epidemic encephalitis, but the latter diagnosis had to be substantiated by further study, and in the meantime the patient received deep X-ray therapy in the belief that an optic nerve neoplasm might be present.

Vision, however, continued to decline and on October 20, 1925 the following observations were recorded: V.O.D. fingers at five feet, V.O.S. $\frac{1}{18}$ minus with relative temporal hemianopsia. The scotoma in O.D. had become much larger (Chart 5). The field for form was still good in both eyes. From now on, however, the impairment of vision became more rapidly progressive and total blindness in

both eyes was threatening. It was then decided to send the patient into a hospital for a serological test and foreign protein therapy.

On admission to the hospital November 2, 1925, the following positive findings were recorded: Right facial weakness, generalized hyperreflexia, biceps, triceps and knee jerks more active on the left, lost lower abdominals and a right Babinski sign. Spinal fluid was negative in all phases. The first days in the hospital the patient's V. continued to fail, so that patient, describing his condition in his own words, had to feel around for different articles of food when meals were served, could not use his knife and fork and he could not see how and where to cut. On November 7,

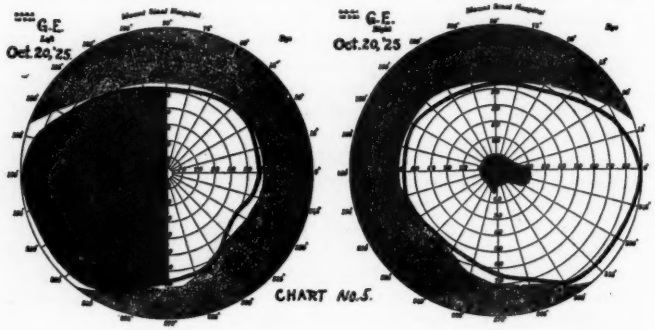


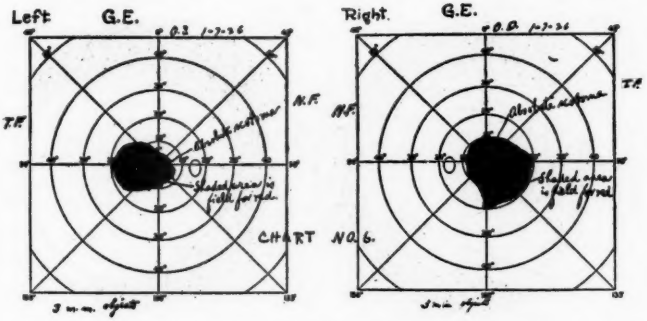
CHART No. 5.

patient was given his first injection of typhoid vaccine, 2 million organisms being injected intravenously. On November 9, he was given the second injection. The following day the patient noted definite improvement in vision, the room was brighter and he began to recognize people who formerly were shadows. With every injection there was a corresponding improvement, so that on November 16 the patient was able to make out large print in papers.

He left the hospital December 5, having received about twenty injections in constantly and gradually increasing doses. On December 8 an examination showed V.O.D. fingers at five feet eccentrically, V.O.S. $\frac{15}{100}$ slightly eccentrically. O.D. showed an absolute scotoma of somewhat oval shape in the lower temporal quadrant, reaching to the fixation point. It was surrounded by a relative area. The absolute scotoma in the left eye was also more on the temporal than on the nasal side and had a relative area around it. The disks still showed good color and the field limits were normal. The injections were continued up to Jan-

uary 30, 1926 and vision in each eye continued to improve. By January 5 O.D. was $\frac{15}{100}$ eccentrically, and O.S. $\frac{15}{100}$ directly. At this time the patient was referred to an out of town ophthalmologist for an opinion and the following observations were made: Vision R.E. $\frac{1}{60}$; L.E. $\frac{1}{180}$; with difficulty, aided by a plus 4.50 sph. he spelled out type M* 1.25, the vision being slightly better in dull than in bright light.

The peripheral field was practically normal in each eye. There was a large relative color (red) scotoma in the right field, extending from near the 10 degree circle on the nasal side temporalward, and especially down and out to the 20 degree circle; the normal blind spot was not enlarged, but

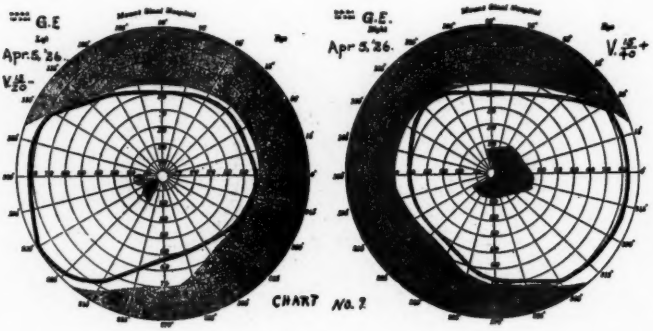


including the fixing point there was a dense absolute scotoma extending below the horizontal to the 5 degree circle. There was in the left a similar, but smaller relative scotoma for red, extending from the nasal side at the 5 degree circle to the 20 degree circle temporalward, and below to the 20 degree circle, and above to the 10 degree circle: a wedge-shaped absolute scotoma occupied a small area down and out, just toucing the fixing point (Chart 6).

The right disk showed a grey red surface, but pallor in part of the papillomacular area; the left disk more generally pallid except up and in. No special changes in the retinal vessels. No definite opinion was expressed by the consultant as to the etiology. Alcoholism, multiple sclerosis, tumor, chiasmal neuritis were considered, with alcohol as the most probable causative factor; the prognosis was thought to be rather gloomy.

Treatment with typhoid vaccines was continued and improvement in vision progressed. On February 2, 1926, the patient left for a trip to California. He was instructed to take small quantities of strychnine, but having taken

half a dozen of these he discontinued. On return from his trip he received five more injections and on April 5, 1926, his vision showed the following: O.D. $\frac{1}{4}\frac{6}{8}$ plus, O.S. $\frac{1}{3}\frac{6}{8}$. The right eye showed a small absolute scotoma, a little temporal to the fixation point and a narrow relative zone around it. The left field presented only a small relative scotoma down and out from the point of fixation (Chart 7). Though treatment was completed at this time, improvement in vision continued, so that on October 6, 1926, an examination of visual acuity was $\frac{1}{1}\frac{6}{8}$ full in each eye and only the right eye showed a tiny relative paracentral scotoma.

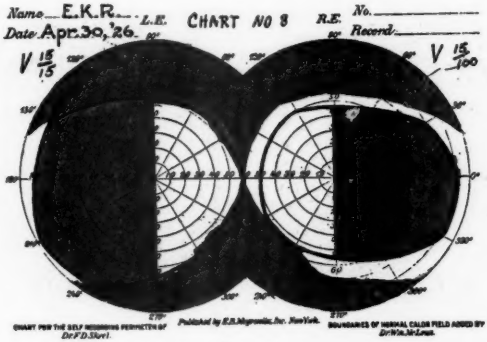


CASE 3.—E. K. R., aged 27, female, unmarried. Her early history is negative except for the common diseases of childhood. At the age of seventeen she had a fall from a horse, but sustained no serious injury, and except for mild concussion she suffered no ill effects. Her eyes were uninjured and her vision was unimpaired. But soon after the accident she developed amenorrhœa and she has not menstruated since.

Her present illness dates back about four years, when on awakening one morning she noticed a decided blurring of vision in the right eye. She consulted an eye specialist who found nothing abnormal. She was referred for a nose examination which was reported negative. X-ray of the head at that time was reported as showing no decided involvement of the sinuses, but the sella turcica was thought to be somewhat increased in size without any evidence of erosion. The visual disturbance of the patient took the form of an hemianopsia, for the patient described it as though "objects were cut in half." A number of visual

fields were taken by a prominent neurologist and showed some visual field defect, but this gradually disappeared and within a period of a few months vision became normal without any therapeutic measure having been employed. Another X-ray examination of the head six months after the onset of the visual disturbance showed no change in the size of the sella turcica.

The patient remained free from symptoms up to the early part of 1926. In February, 1926, she again noticed blurring of vision in the right eye. There was no headache, no dizziness, no vomiting; and, trusting to eventual spontaneous recovery, she consulted no physician. The expected improvement did not occur, and on April 28



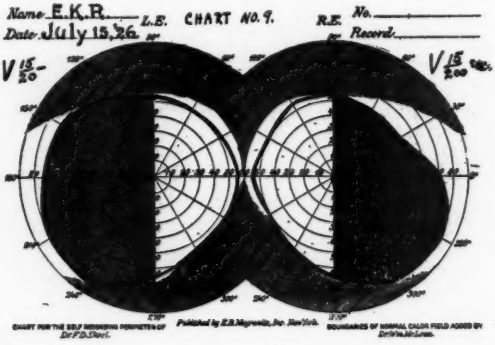
1926, she came for an eye examination. The latter revealed normal pupils, normal discs, but V.O.D. was $\frac{15}{100}$, not improved with glasses, and V.O.S. was $\frac{15}{6}$. The visual fields showed: in O.D. narrowing on all sides of a few degrees for form, and a moderate but unmistakable reduction of clearness of vision in the temporal field as compared with the nasal. The O.S. showed normal limits and a somewhat less marked relative temporal hemianopsia (Chart 8). An X-ray of the sella on May 18 showed no appreciable change from that of four years ago. She was then examined by Dr. Globus for a neurological survey, and all that could be found was a slight congenital facial asymmetry of no diagnostic value.

The absence of positive findings was regarded as a deciding factor in ruling out a cerebral neoplasm. The exclusion of a cerebral tumor was further supported by the absence of symptoms of increased intracranial tension, such as headache, vomiting and papilledema. The only point in favor

of an adenoma of the pituitary was the amenorrhœa and the relative bitemporal hemianopsia. The suspicion of an inflammatory chiasmal lesion was expressed, but there were not sufficient data to support it.

The patient's vision declined rapidly to O.D. $\frac{1.5}{200}$ eccentrically, and in O.S. to $\frac{1}{10}$ minus, with a central scotoma now present in O.D. In view of the progressive impairment of vision and the uncertainty of diagnosis the patient was given the benefit of six deep X-ray treatments without any favorable results (Chart 9). The administration of iodides was resorted to, also without benefit to the patient.

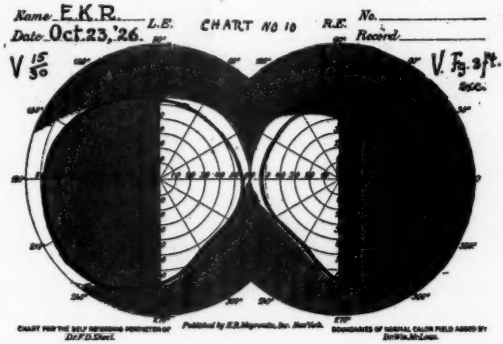
At this time a neuro-surgeon was consulted, who was



inclined to the diagnosis of a benign pituitary neoplasm, and advised subcutaneous injections of pituitrin and the administration of thyroid by mouth. The patient received this treatment for five weeks, up to October 6, but still a further decline in vision was noted. In O.D. vision was reduced to counting fingers eccentrically at six feet; in O.S. to $\frac{1}{10}$. The temporal hemianopsia in the left, the better eye, was now absolute for red, but still relative for white. Vision continued to decline, and in the middle of October, 1926, O.D. could only count fingers eccentrically on the nasal side at three feet. In O.S. vision was $\frac{1}{10}$ with absolute hemianopsia for white as well as for red (Chart 10). In O.D. the larger part of the temporal field was lost, only a relative area remaining in the lower outer quadrant. At this time the patient complained of a heavy feeling in the head and occasional headache. The progressive decline of vision demanded definite therapeutic measures, and it was decided to perform without delay a transfrontal

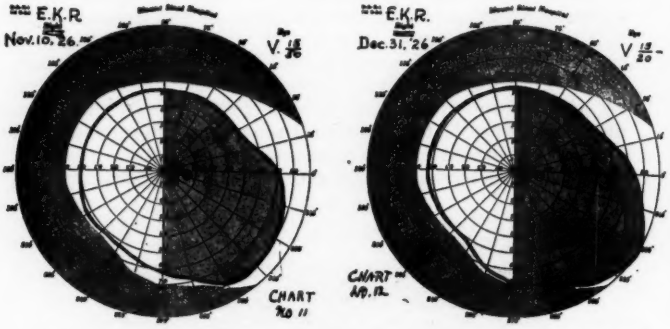
exploratory craniotomy to reach the pituitary region. Two days before the time set for the operation, however, the patient developed a coryza with a febrile state. Soon after this short period of illness an improvement in vision was observed, O.S. showing now $\frac{1}{3}\frac{5}{8}$, while with O.D. she could count fingers eccentrically at six feet. It was assumed that this slight improvement, the only one thus far observed, was due to the febrile attack, which, it was supposed, had stirred up some defensive reaction not unlike that obtained by the administration of foreign protein. It was then deemed advisable to postpone the contemplated operation and to try foreign protein injections.

The first injections were given on October 25 and 27, and



the eye examination on October 29, showed decided improvement in vision. O.S. now showed V. of $\frac{1}{1}\frac{5}{8}$ minus with some hesitation. The injections were given at intervals of two, later three, then four, five and six, and finally seven days. They were given in graded doses beginning with two million and reaching the maximum of 100 million organisms. Each injection was followed by a good febrile reaction and by definite improvement in vision, as will be seen in the following protocol: The vision which, just before the contemplated operation, was O.D. fingers eccentrically at three feet and in O.S. $\frac{1}{1}\frac{5}{8}$, had risen by *November 1* to O.D. $\frac{1}{2}\frac{5}{0}\frac{5}{0}$, O.S. $\frac{1}{1}\frac{5}{8}$. Patient observes that letters are read with much greater ease and rapidity. The absolute scotoma in O.S., recently noted, is also smaller. *November 5*, paracentral scotoma in O.S. now much smaller and difficult to find; vision in O.D. one letter in $\frac{1}{1}\frac{5}{0}\frac{5}{0}$. *November 10*, O.D. with sph. minus 0.50D. three letters in $\frac{1}{1}\frac{5}{6}$; O.S. $\frac{1}{1}\frac{5}{8}$. The absolute scotoma in the right eye is now paracentral and only

six to eight degrees wide. The temporal field still shows relative hemianopsia (Chart 11). *November 15*, O.D. two letters in $\frac{1}{15}$ line. *November 22*, with slightly eccentric vision and studying reads three letters in $\frac{1}{8}$ line. Since then the



vision has improved to $\frac{1}{8}$ plus in O.D., a slight degree of hemianopsia still being present. V.O.S. $\frac{1}{15}$, no hemianopsia, not even relative.[1]

General Considerations.

The three cases we have presented are of interest, first, because of the location and nature of the lesion, and second, because of the unusually favorable results obtained with foreign protein treatment.

Little need be said about the location of the disease process for the character of the visual fields throughout the clinical course of each case in this group points to a lesion in or about the optic chiasma.

Much more difficult is the determination of the character of the lesion; is it of a neoplastic or inflammatory nature?

The positive objective neurological findings have certainly been too meager to justify the diagnosis of an intracranial tumor. Of still greater significance was the absence of any of the cardinal signs of cerebral neoplasm. To be sure, tumors in the pituitary region such as adenoma of the pituitary gland and even many supersellar neoplasms often fail to show

[1] Since the reading of this paper the patient has received further treatment of the same kind, and vision in O.D. is now $\frac{1}{15}$ minus.

signs of increased intracranial tension, and may also lack the typical features of pituitary disfunction; but such cases show commonly, fairly pronounced hemianopsic disturbances.

Recently chiasmal lesions, not pituitary in origin, were described by Lillie (3) and gliomata of the chiasma as well as so-called prechiasmal intracranial tumors were reported by Cushing (4) and Dandy (5) respectively. But these chiasmal lesions were associated with one or more of the following manifestations, which, in order of their frequency are: optic atrophy, pituitary disfunction, sella turcica changes, papilledema and, at times, other features of increased intracranial tension.

There was, of course, nothing in the clinical picture of our cases which would permit of grouping them with such a form of chiasmal involvement.

Thus we were led to believe that the most likely character of the lesion in our cases is a form of a subacute inflammatory process around the chiasma, presenting in addition in two of the three cases evidence of a fairly wide-spread cerebral disease. Case 1 and Case 2 may, with a fair degree of certainty, be classed with a form of subacute epidemic encephalitis, described by Globus and Strauss (6). This form of encephalitis is characterized by latent development of disseminated signs and symptoms, the occurrence of atypical features, which may include also disturbances in the visual apparatus, and by remissions and recurrences. Such diagnostic possibility is, in our opinion, supported by the beneficial effect of the protein therapy; for it is hardly possible that a brain tumor would yield to such form of treatment.

Summary.

The points that these three cases have in common are:

1. Progressive loss of vision, first in one eye, then in the other, without intraocular changes, even at the height of the development of the clinical manifestations.

2. The development of gradually enlarging central scotomata.

3. The development of hemianopsic fields, even though only relative in degree, and requiring careful perimetric examination for their detection.

4. Diagnostic difficulties presented even to expert ophthalmological and neurological consultants.

5. The lack of response to the usual forms of treatment of retrobulbar lesions of the optic nerves.

6. Absence of a toxic etiology.

7. The prompt and progressively favorable response to the intravenous injection of typhoid vaccine.

While these three cases, especially in the absence of pathological evidence, are far from sufficient in number to draw definite conclusions therefrom, nevertheless they have points in common, enough to suggest a clinical entity which might be designated a *chiasmal perineuritis*, that may exist alone or in combination with other neurological manifestations.

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OCULAR DISORDERS IN DEFICIENCY DISEASES.

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Introduction.

THE rapid growth in our knowledge of deficiency diseases during the last decade has made it difficult to digest and properly evaluate the data which has accumulated. This is particularly true from the standpoint of the ophthalmologist, for much of the experimental work, being done by physiologists or chemists, is not to be found in ophthalmological journals, and one must often read much that pertains to growth and metabolism in general in order to extract a few facts concerning the eyes.

This review is intended, therefore, to bring together the results of experimental and clinical study of deficiency diseases only as they affect the structure and function of the eye. For a review of the subject in general the reader is referred to the following recent monographs and books.

1. *The Vitamines*—American Chemical Society; Monographs, by Sherman and Smith.
2. *Newer Knowledge of Nutrition*—Macmillan Co., 3rd Edition, 1925, by McCollum and Simmonds.
3. *Vitamine Manual*, by Eddy.
4. *The Vitamines*—2nd Edition, English translation, 1924, by Funk.

I. Xerophthalmia.

Before the presence of those accessory food stuffs which we call vitamines was suspected, certain diseases were ascribed by clinicians to a lack of something in the diet. This was not only true of general diseases, for example beriberi, and scurvy, but certain diseases marked by eye symptoms were

attributed by ophthalmologists to an ill-balanced or deficient diet.

Thus, Gama Lobo (39) in 1865 described a disease of the eyes occurring among poorly nourished slaves on the coffee plantations of Brazil as the so-called Ophthalmia Brasiliana, —Mori (51) in 1896 reported an epidemic in Tokio of a severe inflammation of the conjunctiva and cornea popularly known as 'hikan" due to an absence of fat in the diet, and still other ophthalmologists have ascribed the high incidence of certain inflammatory eye diseases in Russia during the lenten fasts to the insufficient and poor food. The description of the changes in the eyes in these cases suggest that they were all similar to what we now call "xerophthalmia or keratomalacia."

It is remarkable that as early as 1857 Livingstone (quoted by McCollum and Simmonds), (38) described an affection of the eyes in members of his party during the explorations in Africa and stated "that the eyes became affected (as in the case of animals fed on experiment on pure gluten or starch)."

A somewhat similar disease was produced in the eyes of rats experimentally, by Falta and Noeggerath (15) in 1906 and by Knapp (34) in 1909, although the fat soluble vitamine had not then been discovered; the first definite proof of the existence of this substance having been given by Gowland Hopkins (31) in 1912. It was not until 1913 that Osborne and Mendel (55) produced the disease in its characteristic form and showed that it was caused directly or indirectly by a diet deficient in a certain "accessory substance in the diet." The deficient factor by this time had come to be known as "the fat soluble A vitamine," and Osborne and Mendel showed that xerophthalmia produced experimentally in rats could be cured by adding butter fat (55) or cod liver oil (56) to the deficient diet. Since then the occurrence of xerophthalmia among rats has come to be regarded as a criterion for the adequacy or inadequacy of vitamine A in the diet.

Goldschmidt (20), Stephenson and Clark (66), McCollum and Simmonds (43), Freise, Goldschmidt and Frank (17), have all described a type of ophthalmia in rats which resulted when the animals were restricted to a diet containing insufficient amounts of vitamine A. After 4 to 6 weeks on such a diet the rats begin to have swelling of the lids of one or

both eyes. The lids lose the hair at the margins and lacrymation is often evident. A discharge follows, at first hemorrhagic, later becoming purulent. Finally the cornea becomes cloudy, ulcerates and the eye is lost. The picture of human xerophthalmia, on the other hand, is usually ushered in with the occurrence of local plaques on the conjunctiva of a white material resembling soap suds, the so-called xerosis conjunctivae or Bitot's spots. Then follows the cloudiness and softening of the cornea with ulceration and loss of the eye. The acute purulent symptoms are seldom seen.

In support of the contention that human xerophthalmia and that of the rat are identical in origin is the report of a series of human cases in Denmark by Bloch (6). In an institution for children there occurred an outbreak of xerophthalmia in one particular division when all the other divisions escaped. The diet of all the divisions was the same with the exception that in the one affected the children received no butter, eggs, cream or whole milk. Rapid recovery took place when cod liver oil was added to the diet. In a later paper Bloch (5) reported a study of all of the cases of xerophthalmia admitted to the State Hospital in the period 1912–1919. There was a steady rise in the number of cases until 1917 when there was an abrupt fall and since then practically no cases have been seen.

Widmark (78) points out that although Denmark is famed for its dairy products, practically all the butter is exported so that the poorer classes substitute margarine in the diet for butter. This practice was becoming more prevalent judged by the increasing annual consumption of margarine until 1917, when in December of that year it became necessary for the government to take over the control of all the butter exported owing to the German submarine blockade. Butter was rationed so that everybody received 250 grams a week and it was sold at such a low price that even the poor could buy it. From that moment everyone ate butter instead of margarine and xerophthalmia practically disappeared.

Blegvad (2) has studied the diets of all the cases of xerophthalmia he met with during the years 1909 to 1920 and noted that in all but a few cases when this disease occurred the diet contained none of the foods rich in the fat soluble vitamine.

In the few exceptions to this there were severe gastro-intestinal diseases present which according to his interpretation signified that the children could not assimilate the fat soluble vitamine. A further study of the incidence of this disease revealed the fact that it generally occurs in the Spring, the time when the growth curve is at a maximum as shown by Malling-Hensen. It is well known that in rats the disease is easiest produced during the period of greatest growth.

From the clinical aspect then, the condition in man is similar to that seen experimentally in the rat in its occurrence in the young, during the period of most rapid growth and when the diet is poor or altogether lacks the fat soluble A vitamine. It does not occur in all of a series of rats kept on such a diet, however, and it is probably even more difficult to produce in man, as Hess and Unger (25) have pointed out. They failed to produce the eye changes in five infants kept on a dietary that was complete in every respect except for a lack of the fat soluble vitamine. McCollum and Simmonds (44) point out, however, that the assumption of Hess and Unger (25) that the diet employed was nearly devoid of vitamine A is erroneous. Ross (61) reports four cases of keratomalacia from the Children's Department of the Johns Hopkins Hospital. These were the only cases which occurred in more than 2,800 admissions.

In this respect it is of interest to note that the incidence of the disease in rats kept on a vitamine free diet varies greatly according to different investigators. Stephenson and Clark (66) produced the disease in only 28% of their rats, Osborne and Mendel (57) in 50%, Emmett (14) in 98% of rats, whereas Holm (28) produced the disease in 100% of his experimental animals. This led Walker (76) to question whether there is a definite relation of the fat soluble A to xerophthalmia, because the disease could not be produced readily and in all cases, and he argues that an hereditary predisposition might explain the widely variable and anomalous results. It seems more likely, however, that the varying nature of the diets used might well account for such variations. Stephenson and Clark (66) pointed out that xerophthalmia might not be a deficiency disease in the strict sense of the term. They present certain postulates which they believe

are necessary to establish before applying the term to this disease:

1. That the determining cause is not bacterial infection.
2. That in one species at least the symptoms invariably result from a prolonged course of diet deficient in the fat soluble factor.
3. That identical symptoms never occur as a result of any form of malnutrition in which the fat soluble factor is adequately supplied in the diet.
4. That the symptoms invariably disappear when the factor is replaced in the diet unless death occur.
5. That the symptoms are not susceptible of cure by any treatment other than the supply of the fat soluble factor.

It is almost certain that the determining cause is not primarily bacterial infection although it is almost as certain that part of the clinical picture is caused by an invasion of microörganisms in tissues whose resistance is low. The organism which is found in one stage of human xerophthalmia, namely the xerosis bacillus is a constant inhabitant of many normal conjunctiva and cannot, therefore, be the cause of this disease. Its behavior in culture media moreover is that of a saprophyte and when inoculated into man or animals does not reproduce xerosis of the conjunctiva. Mayou (41) has pointed out that it is comparable in many respects to the smaegma bacillus. In fact, Mayou believes that it is an identical organism and that the conjunctival cul-de-sacs become infected during birth.

Bulley (8) reported that no xerophthalmia occurred in a series of rats on a vitamine free diet if the rats were kept under the very cleanest and healthiest condition and if the eyes were carefully washed with boric acid to prevent infection. Stephenson and Clark (66) however, reported later from the same laboratory that Bulley's experiments were carried on during the war when the caseinogen used for the experimental diets was insufficiently extracted with alcohol so that the diet was not absolutely free from vitamine A.

Emmett (14) attempted to transmit the disease by taking sterile threads of gauze and passing them cautiously over the edge of the lids of the xerophthalmic eyes and then inoculating the eyes of other healthy rats. These tests were negative.

Findlay (16) attempted to produce keratomalacia by inoculation of bacteria from the conjunctival sac of the affected rats into normal healthy eyes. Stephenson and Clark (66) had already shown that the bacterial flora was no different in the xerophthalmic rats than in the normal control rats, but Findlay suggested that it was still possible that in keratomalacia the organism might have an increased virulence. The inoculation of bacteria, however, as carried out by Findlay resulted in no development of keratomalacia nor did the same material when injected into rats kept on a diet free from vitamine A hasten the onset of keratomalacia in these rats.

Findlay (16) carried his experiments still further. He pointed out that Flemming and Allison had shown a powerful lytic action of human tears on certain bacteria. He set about to determine, whether there was any change in the lysozyme of the tears and of the blood serum of rabbits fed on diets lacking in vitamine A. In a small series of rabbits there was a definite decrease in the lysozyme content of the tears at the onset of keratomalacia whereas there was little or no fall in the lysozyme content of the blood serum. The evidence, therefore, is all against this being due to bacterial infection primarily, whereas the last mentioned experiments of Findlay give further suggestive evidence that certain changes go on in the body as a result of the disease whereby the resistance of the tissues to infection is lowered.

It has already been pointed out that the symptoms of keratomalacia have not invariably appeared from a prolonged course of diet deficient in the fat soluble factor, but this argument does not seem as weighty as several of the others. It is of far greater import to determine whether or not the identical symptoms of keratomalacia ever occur as a result of any form of malnutrition in which the fat soluble factor is adequately supplied in the diet. In 1922 McCollum, Simmonds and Becker (46) described a type of ophthalmia in rats which resulted when the animals were restricted to a diet containing amounts of butter fat sufficient to furnish the vitamine A to meet the physiological need of the animal during growth. The ophthalmia was shown to be produced by the character of the inorganic moiety of the diet. In this paper it was suggested that the disease might have been due

to an excess of chlorine and possibly an excess of sodium in the diet and the ophthalmia was spoken of as "salt ophthalmia," but Mori (52) concluded from a histological study of the eyes and related structures in these rats that the anatomical changes were identical to those seen in the ophthalmia caused by a deprivation of vitamine A.

These same authors in 1925 (45) reported further that the ophthalmia could not be produced by adding an excessive amount of any one element or ion to the diet and that therefore their former surmise that the ophthalmia was due to excess amounts of chlorine or possibly of sodium in the diet was untenable. It appeared to them that the total amount of a salt mixture and its composition might be the determining factor as to whether the ophthalmia did or did not develop.

This presents a most serious obstacle to pronouncing xerophthalmia a definite deficiency disease. There are no other reports in the literature of xerophthalmia being caused experimentally by other diets save those deficient in vitamine A, and no attempt has been made as far as we are aware to repeat the work of the last mentioned authors. From the clinical side, however, it has recently been seriously questioned whether keratomalacia is caused exclusively by a lack of vitamines. Fuchs, A. (quoted by Stransky) (70) showed a two-year-old child fed on a correct diet who had received cod liver oil from 7 to 14 months of age and who had developed a severe keratomalacia of both eyes. At the same meeting Pillat also showed a similar case. Czerny (10) and Keller look upon this disease as a terminal phenomenon of faulty carbo-hydrate metabolism. Schiff (63) questions the propriety of comparing the results of animal experimentation with the disease as it arises in human beings. Genck (19) cites a case where xerophthalmia occurred in spite of a diet rich in vitamine A.

In order to bring out more clearly the etiology of this disease in human beings Stransky (70) collected six cases. In five of these cases there could be no question of a deficiency of vitamine A in the diet but the etiology was plainly primarily a question of lowered resistance from one cause or another. In one case a child with a pyloric stenosis developed the disease while breast fed. Stransky claims that in this case

we are dealing with mere quantitative inanition. One of twin children fed on the same diet containing plenty of vitamine A showed the development of the disease when it contracted pneumonia. It is interesting to note that in several of the cases vitamine therapy did not improve the condition.

In all the reports of keratomalacia produced experimentally the symptoms have invariably disappeared when the fat soluble A vitamine was added to the diet unless death ensued. It is unfortunate that in the "salt ophthalmia" produced by McCollum, Simmonds and Becker (46) no attempt was made to treat the disease by either supplying more vitamine to the diet or by changing the salt content.

The final postulate of Stephenson and Clark (66) that the symptoms should not be susceptible of cure by any other than the supply of the fat soluble factor should not weigh very heavily as proof that this is or is not a deficiency disease. It is quite possible that the same effect might be produced in the body by other substances and other means than the fat soluble vitamine. Powers, Park and Simmonds (60) studied the influence of radiant energy upon xerophthalmia. Young growing rats were placed on a diet which was known to produce both rickets and xerophthalmia. They were divided into four groups, each of which was subjected to a different condition of light, namely:

1. Ordinary room light (window glass; 2. darkness; 3. room light plus ultra violet lamp radiation (30 minutes exposure per day); and 4. direct sunlight, average exposure 4 hours a day.

Similarly a second group of rats were placed on a diet which produced xerophthalmia alone, and these were treated in the same manner. On both diets the rats in the ordinary room light, darkness, and ultra violet lamp groups developed xerophthalmia early. Exposure to the quartz mercury vapor lamp, 30 to 60 minutes daily did not prevent the development of xerophthalmia. The rats which were exposed to direct sunlight, however, with one exception, never developed xerophthalmia until the animals in the other groups had developed the disease and died. In some of these rats exposed to sunlight the disease was of a mild recurring nature and in two rats the xerophthalmia did not appear at all. It seems,

therefore, that exposure to direct sunlight protects rats from xerophthalmia to a limited degree.

These authors state, however, that "sunlight possibly exerts no specific anti-xerophthalmic influence but acts by raising the level of the cellular activity of the organism to a point where the onslaughts of the disease are held in check or allowed to advance very slowly and with relatively little disturbance."

The histological pathology of the eye lesions has recently thrown light upon the question. Stephenson and Clark (66) and Wason (77) failed to find any characteristic changes in the cornea preceding bacterial invasion. Freise, Goldschmidt, and Frank (17) noted an early cornification of the epithelium and Mori (49) also describes cornification of the outer layer of epithelial cells of the bulbar conjunctiva together with the formation of granules of keratohyalin in the cytoplasm in the second layer of these cells. The deposition of keratohyalin did not occur in the cornea proper but only at the limbus.

Mori (49) believed that these changes preceded the invasion by bacteria. In a later paper Mori (50) studied the changes in the lacrymal glands and concluded that these showed the most important changes of the whole pathological picture. His studies indicated that little if any secretion was produced by the lacrymal glands of xerophthalmic animals and both the Meibomian and Harderian glands also showed characteristic changes. He found further changes in the salivary glands and he mentions xerotic changes in the mucous membrane of the respiratory tract. Mori (50) concluded that the clinical picture of xerophthalmia should be considered a series of secondary symptoms indicative of hypofunction of certain secreting cells. He believed, therefore, that the changes in the cornea were due directly to the drying of the eye causing a resultant cornification of the epithelium.

Yudkin and Lambert (35, 36, 82, 83) could not confirm Mori's conclusions. They consider the earliest lesions to be foci of inflammation in the lids, chiefly near the palpebral fold. The corneal involvement they regard as secondary to these lesions which they assume are in the nature of a bacterial infection. Manville (40) was able to confirm Mori's results that there

was a lack of secretory activity on the part of certain glands and he shows that the changes are not limited to the paraocular glands but that the secretions of the gastro-intestinal and genito-urinary tracts are also lessened.

Dötsche (12) studied the histological pathology in two cases of keratomalacia in infants and showed thickening of the conjunctival epithelium most marked near the limbus. True cornification took place in one case. The usual picture of corneal ulcer follows. Finally the very complete study of Wolbach and Howe (80) shows that "the specific tissue changes which follow the deprivation of fat soluble vitamine A in albino white rats and in the human concerns epithelial tissues. This effect is the substitution of stratified, keratinizing epithelium for normal epithelium in various parts of the respiratory tract, alimentary tract, eyes, and paraocular glands, and the genito-urinary tract." They have shown "that the substitution of keratinizing epithelium in all locations is not secondary to infections, and presumably is a primary effect of the withdrawal of factors essential for the chemical activities or maintenance of differentiation of the epithelial cells." Thus, it is seen that feeding a diet deficient in vitamine A results in manifold changes in the body, the eye symptoms of which are only a part of the general pathology. This pathology, however, is typical for all epithelial structures. At the present time a good deal of experimental work with vitamines indicates that changes in intestinal absorption *i.e.*, in permeability, are associated with vitamine deficiency and may be responsible for many of the manifestations of this disease. Park (58) has stated that one at least of the functions of vitamines appears to be the protection of the organism from the dangers attending on the absorption and entrance into the blood of substances which might disturb its salt balance and Cramer (9) has suggested that the whole vitamine activity is dependent on the intestinal wall changes producing a secondarily deficient or altered absorption and an increased local susceptibility to infection. Kagoshima (33) believes that a vitamine A deficiency is a true metabolic disease and that the lack of this vitamine leads to a disturbance in calcium metabolism. In addition to the more general phases of vitamine A deficiency above described numerous other

effects have been observed in experimental animals. Damianovich, H., Bianchi, A., and Savazzini, L. A. (11) found that a deprivation of vitamine A or B quickly brought on an anæmia which could be alleviated by the addition of vitamine B to the diet. Hirai (27) found that animals fed on deficient vitamines developed marked hyperglycæmia and Funk and Schonborn (18) ran a short series of experiments on pigeons kept on a vitamine A free diet. When the animals were kept on a sugar free diet there was an entire disappearance of liver glycogen while the addition of vitamine from yeast to the latter diet produced a marked formation of glycogen in the liver and a diminution of sugar in the blood. Vitamine A thus seems to have a distinctive influence on the glycogen metabolism. As McCollum and Simmonds (42) point out "it is doubtful whether a deficiency disease ever occurs uncomplicated in man or animals." Whenever the list of foods available is greatly restricted and the diet unsatisfactory to a pronounced degree the pathological condition produced is a complicated one.

II. Cataracts.

Certain changes in the lens have been thought to be dependent upon a lack of vitamine in the diet. In 1913 Szily and Eckstein (72) found that in a series of young nursing rats the lenses in some of the rats became cataractous when the diet of the mothers was deficient in vitamines.

Stepp and Friedenwald (68) attempted to repeat these experiments in McCollum's laboratory. In four series of animals they produced a total of thirty-four young rats showing various degrees of rickets and even xerophthalmia but in no case were the lenses cataractous. These latter authors fed the mother rats on McCollum's diet #3143 in which there was a lack of the anti-xerophthalmic vitamine A and of the anti-rachitic vitamine D, in addition to deficient phosphates and an excess of calcium. Jess (quoted by Schreiber) (62) was also unable to produce cataracts in a series of rats fed on Hopkin's diet which is entirely free from the anti-xerophthalmic A vitamine.

Szily and Eckstein's (72) experiments have been repeated

by Schreiber (62) in so far as the dietary factor is concerned. The young rats, however, were separated from the mothers and were themselves fed on the vitamine free diet after the nursing period.

Of seven litters containing forty-nine rats there were well-marked changes in a few after eight weeks of experimental feeding. These animals all showed marked general changes including loss of weight, lack of development of the bones, etc. The lenses were examined histologically and although in some the opacity was somewhat similar to the congenital cataracts described by Von Hess (24), Schreiber (62) states very definitely that this form of cataract could not be a form of congenital cataract of rats but must have been due to the deficient diet. No control series are given.

It must not be lost sight of that in any series of experimental animals, and especially in particular strains of such animals, as white rats and certain breeds of rabbits, changes in the lenses are fairly common as a congenital anomaly. It is unfortunate that neither Szily and Eckstein (72) nor Schreiber (62) have examined a series of rats from the same stock as their experimental animals to determine the incidence of cataractous changes in the series fed on normal diets.

III. Night Blindness.

The terms hemeralopia and nyctalopia for this condition have been purposely omitted due to the great confusion which their use creates. It is held by some that the derivation of the word hemeralopia is such as to mean literally day blindness, and therefore is entirely inappropriate for this disease. Its common use in the literature, however, in the sense of blindness under conditions of reduced illumination will hardly allow of any other interpretation. It is best to drop both terms, as they add nothing to our knowledge of the condition, and to use instead the clearly descriptive term night blindness. For a complete discussion of the uses of these terms, see Bordley's (7) paper.

This disease has been described as an accompanying or often a preceding symptom to xerophthalmia and xerosis conjunctivæ. The literature contains numerous case reports occurring among various peoples under conditions of hard

work and poor nourishment, and especially among men exposed to bright sun-light, as in sailors in the tropics.

Night blindness, however, is a symptom and not a disease *sui generis*. It occurs in a variety of diseases and under conditions so varying that it is quite certain its occurrence is not due to one but to many factors. Thus, the various types seen in conjunction with retinitis pigmentosa, syphilitic retinitis, associated with icterus, scurvy, etc., do not have a common cause. It is probable, however, that the pathology or rather the pathological physiology is the same in all these cases. We are dealing with some disturbance in the scotopic mechanism, as Parsons (Introduction to the Study of Color Vision) terms it—some defect in the function of the rods and visual purple.

The association of this condition with xerosis conjunctiva or xerophthalmia is evident from the cases reported by Bitot, Cless, Dumas, Groenow, deGouvea, Adamantiadis (1), and others. It occurs, however, without xerosis of the conjunctiva or xerophthalmia, as in Edmund's (13) case, cases reported by Hess (24), Wagner (75), Ishikara (32), Merz-Weigandt (42) and others. The treatment of this condition which dates as far back as Hypocrates, is to supply the fat soluble A vitamine in some form or other. Hypocrates advised the use of liver in abundance, which is now known to be rich in this principle. In fact Goldblatt and Soames have shown that the fat soluble A vitamine is stored in the liver in about the same proportion as it occurs in the food. Wagner (75) presents four cases which he believes show a certain correlation between the function of the liver and the appearance of xerophthalmia.

Hift (26) observed that the night blindness occurring at the beginning of the war was quickly cured by the addition of liver or cod liver oil to the diet. Ishikara (32) found a low fat content of the blood in twelve cases of night blindness and an increase of fat in the diet led to improvement in the subjective symptoms.

This is fair clinical evidence that some substance present in liver and certain fats is in some way concerned with the rod-visual-purple function. Edmund's (13) remarkable case of a man with severe night blindness who was cured only

after parenteral injections of a concentrated A vitamine in spite of a well balanced diet, illustrates that this substance has marked curative value if it be assimulated by the organism or presented in suitable form. Successful treatment with A vitamine has been carried out by Ishikara (32), Snell, Stenitzer and Schroder, and others.

In order to determine experimentally whether a lack of vitamines in the diet had any effect on the visual purple, Holm and Fridericia (30) carried out a well planned series of experiments in rats. They first attempted to compare the amount of visual purple in the retinæ of experimental rats on a deficient diet with the amount of visual purple in the retinæ of control rats. No difference could be found, however, between the amount of visual purple in the eyes of the control and experimental rats when these rats were kept in a dark room. They argued that it was possible that the regeneration of visual purple might proceed more slowly in rats on a deficient diet and they therefore exposed the eyes of pied rats to brilliant illumination so as to bleach all of the visual purple. The eyes were then removed and opened in a dark room in red light and the color of the retinæ observed. If bleaching was complete in this eye the remaining eyes of each of the two rats were enucleated after the animal had been in the dark for varying periods of time.

The amount of regeneration of visual purple was judged by comparing the color of the retina with an arbitrary scale. It was necessary to instill atropine in the eyes of the pied rats and to narcotize them during the exposure to light. This treatment was carried out alike on the experimental and control series.

In the experimental rats the eyes had to be examined before pronounced symptoms of xerophthalmia appeared because these symptoms are soon followed by keratitis, and opacities of the cornea might impede the effect of the light on the visual purple. Hence, these rats were examined when the weight commenced to decrease and enophthalmus and conjunctival secretion began. The results of these experiments were uncertain. They suggested that the regeneration was a little slower in the experimental rats but the difference was very trivial and in consequence doubtful.

Another series of experiments was undertaken and carried out in the same way but with an additional daily exposure of the rats to light. This series showed a slight delay in the regeneration of the visual purple in the experimental eyes. In order to make this more certain a final series was undertaken using albino rats. In this series it was quite evident that the regeneration of the visual purple was much slower and within the time of observation much more incomplete in the experimental albino rats starved for A vitamine than in the control rats on an adequate diet. From these results they concluded that starvation for A vitamine in rats produced a defect in the function of the visual purple, the defect consisting in a slowness of the regeneration of the visual purple after its having been bleached through exposure to intense light. This abnormality occurs earlier than pronounced symptoms of xerophthalmia. It did not occur in a series of rats who had been starved for vitamine B.

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INDEX OF AUTHORS AND SUBJECTS.

VOL. LVI.

Accommodation Near Point and the Astigmatic Axis, Apparatus for Determining, (T. P. Lee) 351

ADLER, FRANCIS HEED, Ocular Disorders in Deficiency Diseases, 593

ALLING, ARTHUR N., Exfoliation of the Lens Capsule, 1

Amaurosis of Retrobulbar Origin, Cured by Foreign Protein Treatment, 302

Amaurosis, Three Cases of Progressive, of Retrobulbar Origin, Recovery of Vision with Foreign Protein Treatment, (Julius Wolff and Joseph H. Globus) 576

Anterior Chamber Irrigator, 382

Anterior Chamber, Vascular Gelatinous Plaque in Angle of the, 294

BARLOW, AARON, Fundus Changes in Hypertension, With and Without Nephritis, 356

BEACH, S. JUDD, Familial Maculocerebral Degeneration in Half Brother and Sister, 286

BENEDICT, WILLIAM L., VON LACKUM, WILLIAM H., and NICKEL, ALLEN A. C., The Pelvic Organs as Foci of Infection in Inflammatory Diseases of the Eye, 116

BERGMEISTER, RUDOLF, "Die Tuberkuloesen Erkrankungen des Auges," Review of, 517

BLACK, NELSON M., and HAESSLER, F. H., Dystrophic Intracellular Opacity of the Corneal Epithelium, 151

BLANTON, W. B., "A Manual of Normal Physical Signs," Review of, 314

Blindness, Causes of, in Missouri and St. Louis, (H. D. Lamb) 469

Book Reviews, 311, 422, 515

BOTHMAN, LOUIS, and COHEN, SEYMOUR J., Studies in Intraocular Pressure, 110

Buphthalmus in a Boy, 370

BYRD, HIRAM, The Relation of the Nasal Ganglion to Glaucoma, 162

Cataract, Corneoconjunctival Suture for, Operations for, (F. H. Verhoeff) 137

Cataract, The Cause of the Glaucoma of Hypermature, (H. Gifford) 457

Cataract, Treatment of the Iris in Operations for, (Lt.-Col. Henry Smith) 105

Cholesterin in Anterior Chamber, 305

Choroid, Report of a Case of Flat (Infiltrating) Melanosarcoma of the, (James W. Smith), 156

Choroiditis at the Macula, 177

Ciliary Body, Tear into the, from a Contusion, (H. D. Lamb) 332

CLARK, C. F., Changes in Refraction from Study of Case-Records During Four Decades, 52

Clinical Cases, 80

COHEN, MARTIN, and MEEKER, LOUISE H., A Case of Multilocular Cyst of the Optic-Nerve Meninges, 211

Conjunctiva and Cornea, Reports on the, 398

Conjunctiva, Bilateral Xerosis of the, 295

Corneal Epithelium, Dystrophic Intracellular Opacity of the, (Nelson M. Black and F. H. Jaessler) 151

Correspondence, Technique of Intracapsular Extraction, etc., 100, 202, 421
Cross, George H., Removal of a Number Six Lead Shot, within the Eyeball, by Specially Devised Forceps, with the Aid of the Double Fluoroscope, 564
Cyclopic Eye, On the Subjective (The Third Eye), (Sh. Funaishi,) 328
Cysts, Implantation, 481

d'Autrevaux, "Précis de Technique Histo-Bactériologique Oculaire," Review of, 313
Davis, W. T., Vascular Lesions of the Fundus Oculi, 477
Derby, George S., and Carvill, Maud, Anterior Ocular Tuberculosis, 523
Dermoid Tumors, Bilateral, in the Eyes, 306
De Schweinitz, George E., Essential Progressive Atrophy of the Iris, 10
Divergence Excess, Its Diagnosis and Treatment, (John H. Dunnington) 344
Duane, Alexander, Obituary notices of, 66
Dunnington, John H., Divergence Excess, Its Diagnosis and Treatment, 344

Eagleton, Wells P., "Cavernous Sinus Thrombosis," Review of, 311
Endophthalmitis, from Retained Foreign Body Phagocyst, (Derrick T. Vail, Jr., and F. H. Verhoeff) 5
Exophthalmic Goiter, with External Ocular Paresis, 368
Exophthalmos, Unilateral, with Choked Disc, 76
Eye, Anatomical Relations of the, to the Accessory Sinuses of the Nose, 295
Eye, Deficiency Diseases of the, (Francis Heed Adler) 592
Eye, the Nutrition of the, (Andrew Rados) 567
Eyeball, Metaplasia of the Tissues of the, 489
Eyeball, Traumatic Rupture of the, with Expulsion of the Lens into the Conjunctival Sac, 301
Eyebrow, Plastic Operation for, 383

Fuchs Fund, 420
Funaishi, Sh., On the Subjective Cyclopic Eye (The Third Eye), 328
Fundus Oculi, Vascular Lesions of the, (W. T. Davis) 477

Gifford, H., The Cause of the Glaucoma of Hypermature Cataract, 457
Gifford, Sanford R., Fatty Infiltration of the Anterior Segment, (Xanthomatosis Bulbi) 281
Glaucoma, Development of the Scotoma of, (A. H. Thomasson) 319
Glaucoma, How Primary, may Arise from Disturbances in the Physico-Chemical Forces, Regulating Intraocular Fluid Exchange (J. Herbert Waite) 460, 552
Glaucoma, Relation of the Nasal Ganglion to, (Hiram Byrd) 162
Glaucoma Scotoma, (A. H. Thomasson) 381
Glaucoma, Simplified Conception of Visual Field Changes in Chronic, (Luther C. Peter) 337
Glaucoma, 636 Cases of Trephining for, 195
Glaucoma, X-Ray Therapy in Certain Forms of, (Ralph L. Lloyd) 445
Griscom, J. Milton, and Monroe, Margaret M., Visual Field Studies, in a Case of Optic Neuritis, Secondary to Sinus Diseases, 244

Hanke, Viktor, "Das Auge, seine Schaedigungen, ihre Verhuetung, und Bekaempfung," Review of, 520
Herrenschwand, F. V., "Die Pathogenischen Microorganismen des Auges," Review of, 515
Hertel, Prof. B., "Stilling's Pseudo-Isochromatische Tafeln zur Pruefung Des Farbensinn," Review of, 312
Hopkins, J. C., Syphilitic Lesions of the Eye, 500
Hopkins, J. C., The Treatment of the Commoner Syphilitic Lesions of the Eye, 543
Hypertension, Fundus Changes in, With and Without Nephritis, (Aaron Barlow) 356
Hypopyon Ulcer, Treatment of, Discussions on, 493

Illusions, Cases of Ocular, (G. Lindsay Johnson) 465
IMRE, JOSEPH, Protection of the Eyes by Reflecting Glasses, 141
Intracapsular Extraction, Technique of, 207
Intraocular Sarcoma in a Child, 299
Intraocular Tension and Glaucoma, Reports on, 187
Iridocyclitis, Treatment of, by Subconjunctival Injections of Atropin and Epinephrin, (Frank H. Rodin) 277
Iris, A Case of Detachment of the Anterior Layers of the, (Mark J. Schoenberg) 538
Iris, Essential Progressive Atrophy of the, (George E. de Schweinitz) 10
Iris, Implantation Cyst of the, 298
Iris, Post-operative Cyst of, 382
Iris, Traumatic Cyst of, 384
Iris, Traumatic Detachment of Anterior Layers of the, 169

JOHNSON, G. LINDSAY, The Use of the Oblique Muscles of the Eye, 272
JOHNSON, G. LINDSAY, Two Curious Optical Illusions, 465

Keratitis Interstitialis, 502
Keratitis, Organoluetic Reaction in the Diagnosis of Interstitial, (Dohrmann K. Pischel) 249
Keratoconus, 384
Kerato-Irido-Cyclitis, Bilateral, 369
KIRBY, DANIEL B., The Cultivation of Lens-Epithelium "in Vitro," 450, 499
KNAPP, ARNOLD, Observations on Glaucoma in Morgagnian Cataract, 124

LAMB, H. D., A Case of Tear into the Ciliary Body from Contusion, 332
LAMB, H. D., Causes of Blindness in Missouri and St. Louis, 469
Lead Shot, Removal of a Number Six, from Within the Eye by Forceps with Aid of Double Fluoroscope, (George H. Cross) 564
LEE, T. P., A Simple Apparatus for Determining the Near Point of Accommodation and the Astigmatic Axis, 351
Lens, Reports on Diseases of the, 413
Lens Capsule, Exfoliation of the, (Arthur N. Alling) 1
Lens Epithelium, Cultivation of, "in Vitro," (Daniel B. Kirby) 450, 499
Lenticonus, Slit-Lamp Study of Posterior, (Elias J. Marsh) 128, 169
Leprosy of the Eye, Analysis of 512 Cases of, in the Hawaiian Islands, (Forrest J. Pinkerton) 42
Lids and Lacrimal Organs, Reports on Diseases of the, 93
LINDNER, K., "Die Bestimmung des Astigmatismus," Review of, 520
LLOYD, RALPH L., X-Ray Therapy in Certain Types of Glaucoma, 445

Macula, Choroido-retinitis at, 370; Choroiditis at the, 177; Coloboma at the, 178
Maculocerebral Degeneration, Familial, in Half Brother and Sister, (S. Judd Beach) 286
MARSH, ELIAS J., Slit Lamp Study of Posterior Lenticonus, 128
MELLER, J., and HIRSCH, OSKAR, "Ueber die Rhinogene Neuritis Retrobulbaris," Review of, 518
Migraine, Discussion on, British Med. Assoc., 172
Morgagnian Cataract, Observations on Glaucoma in, (Arnold Knapp) 124
Motor Apparatus of the Eye, Reports on, 182
Myopia, Removal of Lens in, for Improvement of Vision in High, 76

New York Academy of Medicine, Report of Proceedings of the Section on Ophthalmology, 64, 169, 294, 380, 499
Nictitating Membrane, Comparative Anatomy of the, 491
NOGUCHI, HIDEYO, Experimental Studies of Trachoma, 423
Notices, English Speaking Ophthalmological Societies, etc., 102, 209, 316, 420, 522
Nystagmus, Discussions on, 371, 491

Oblique Muscles, Use of the, of the Eye, (George Lindsay Johnson) 272

Ocular Disorders from Deficiency Diseases, (Francis Heed Adler) 593
Ocular Syphilis, Discussion on, 374
Operations, Commoner, on the Eye, 385
Ophthalmological Societies, English Speaking, 102
Ophthalmological Society of the United Kingdom, 103
Ophthalmology, Reports on the Progress of, 87, 182, 387, 504
Ophthalmoplegia, Chronic, and Ptosis, 368
Optic Atrophy, 502
Optic Atrophy and Tower Skull, 380
Optic Nerve, Abscesses of the, (Algernon B. Reese) 265
Optic Nerve Meninges, Multilocular Cyst of the, (Martin J. Cohen and Louise H. Meeker) 211
Optic Nerves, Bilateral Evulsion of Both, 78
Orbit, Lymphangioma of the, 77
Orbit, Neoplasm of, Cured with Radium and Followed with Cataract, 74
Orbit, Sarcoma of the, 304
Orbit and Eyeball, Rod Palpatory Method Exploration of Some of the Contents of the, and Surface of the, (Mark J. Schoenberg) 438
Orbits and Accessory Cavities, Reports on Diseases of the, 87
Oxford Ophthalmological Congress, 209

Parsons, Sir John Herbert, "Diseases of the Eye," Review of, 518
Pelvic Organs as Foci of Infection in Inflammatory Diseases of the Eye, (William L. Benedict, William H. Von Lackum, and Allen A. C. Nickel) 116
Peter, Luther C., A Simplified Conception of Visual-Field Changes in Chronic Glaucoma, 337
Pinkerton, Forrest J., Leprosy of the Eye, an Analysis of 512 Cases of, in the Hawaiian Islands, 42
Pischel, Dohrmann K., The Organoluetin Reaction in the Diagnosis of Interstitial Keratitis, 249
Pressure, Studies in Intraocular, (Louis Bothman and Seymour J. Cohen) 110
Protecting Lenses, 171

Rados, Andrew, The Nutrition of the Eye, 567
Reese, Algernon B., Abscesses of the Optic Nerve, 265
Reflecting Glasses, Protection of the Eyes by, (Joseph Imre) 141
Refraction, Changes in, from a Study of Case Records during Forty Years, (C. F. Clark) 52
Retina, a Case of Apparently Cured Glioma of the, 78
Retina, Angioid Streaks of the, 305
Retina, Detachment of the, 78
Retina, Glioma of the, Cured by Radium Treatment in the Non-Enucleated Eye, (Mark J. Schoenberg) 221
Retinal and Choroidal Diseases, Classification of, 78
Retinal Artery, Bilateral Prepapillary Vascular Loop of the, (Arthur M. Yudkin) 474
Retinal Petechiasis, from Auto-Intoxication, 307
Rodin, Treatment of Iridocyclitis by Sub-conjunctival Injections of Atropin and Epinephrin, 277
Roenne, Henning, On the Mechanics of the Squint Operation, 428, 503
Rollet, E., and Colrat, A., "Tuberculose de l'Oeil et de ses Annexes," Review of, 516
Royal Society of Medicine. Transactions of the Ophthalmological Section of the, 80, 177, 304, 368

Sarcomas and Gliomas, Slides of, 384
Schiff-Wertheimer, Susanne, "Les Syndromes Hemianopsiques dans le Ramolissement Cerebral," Review of, 313
Schoenberg, Mark J., A Case of Detachment of the Anterior Layers of the Iris, 538
Schoenberg, Mark J., Report of a Case of Bilateral Glioma of the Retina, Cured in the Non-enucleated Eye by Radium Treatment, 221
Schoenberg, Mark J., Rod Palpatory Method for the Exploration of Some of the Orbital Contents, and of the Surface of the Eyeball, 438
Sight and Refraction, Reports on, 387
Smith, Lt.-Col. Henry, The Treatment of the Iris in Cataract Operations, 105

SMITH, HOMER E., "Applied Refraction," Review of, 422
SMITH, JAMES W., Report of a Case of Flat (Infiltrating) Melanosarcoma of the Choroid, 156
Socket, Operation for Contracted, 490
Squint Operation, On the Mechanics of the, (Henning Roenne) 428, 503
STOKES, JOHN H., The Principles of Syphilotherapy as Applied to the Eye, 229
Syphilitic Lesions of the Eye, (Hopkins, J. C.) 500
Syphilitic Lesions, Treatment of the Commoner, of the Eye, (J. C. Hopkins) 543

TAYLOR, W. S., and JASTROW, JOSEPH, "Readings in Abnormal Psychology and Mental Hygiene," Review of, 314
THOMASSON, A. H., The Development of the Glaucoma Scotoma, 319
Trachoma, (H. Noguchi) 503
Trachoma Amongst the Indians, 202
Trachoma, Experimental Studies of, (Hideyo Noguchi) 423, 503
Trachoma, Operative Treatment of, 205
Tuberculosis, Anterior Ocular, (George S. Derby and Maud Carvill) 523

United Kingdom, Report of the Annual Congress of the Ophthalmological Society of the, 489
Upper Lid, A Case of Adenoma Carcinoma of the, Subsequently Extending into the Orbit, (Herbert Wright Wootton) 275, 294
Uveal Tract, Reports on the, 504
Uveitis, An Effective Treatment for Sympathetic, (F. H. Verhoeff) 28

VAIL, DERRICK T., JR., and VERHOEFF, F. H., Endophthalmitis from Retained Foreign Body Phagocyst, 5
VERHOEFF, F. H., An Effective Treatment for Sympathetic Uveitis, 28
VERHOEFF, F. H., Corneo-conjunctival Suture for Cataract Operations, 137
VERHOEFF, F. H., Commoner Operations on the Eye, 385
Vienna, Post Graduate Courses in, 316
Visual Field, Studies of, in a Case of Optic Neuritis, Secondary to Sinus Disease, (J. Milton Griscom and Margaret M. Monroe) 244
Vitreous, Foreign Body in the, 306

WAITE, J. HERBERT, How Primary Glaucoma may Arise from Disturbances in the Physico-Chemical Forces which Regulate Intraocular Fluid Exchange, 460, 552
WOELLFLIN, E., "Tafeln mit Umschlagsfarben zum Nachweis von Relativer Rot und Gruensichtigkeit," Review of, 312
WOLFF, JULIUS, and GLOBUS, JOSEPH H., Three Cases of Progressive Amaurosis of Retrobulbar Origin, Recovery of Vision with Foreign Protein Treatment, 576
WOOTTON, HERBERT WRIGHT, A Case of Adenoma Sarcoma of the Upper Lid, Subsequently Extending into the Orbit, 275, 294

Xanthomatosis Bulbi (Fatty Degeneration of the Anterior Segment), (Sanford R. Gifford) 281

YUDKIN, ARTHUR M., Bilateral Prepapillary Vascular Loop of the Retinal Artery, 474

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